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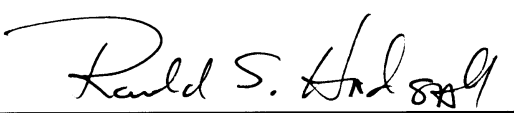

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DAILY MIGRAINE PREVENTION AND ITS INFLUENCE ON RESOURCE UTILIZATION IN THE MILITARY HEALTH SYSTEM

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL OF THE UNIVERSITY OF MINNESOTA
BY

JOSHUA W. DEVINE

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

RONALD S. HADSALL, ADVISER

AUGUST 2006

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ABSTRACT

Migraine is a widespread and disabling neurological disorder with a substantial economic burden due to the frequency and severity of the disease. Daily migraine prevention is recommended for patients who experience regular migraine headaches. While the safety and efficacy of this treatment has been established, it is unclear what impact migraine prevention has on health care resource consumption. This study was undertaken to determine if the initiation of daily migraine prevention had an effect on ambulatory health care utilization compared to acute migraine treatment alone.

Administrative claims data from the Military Health System were used to conduct a retrospective, longitudinal cohort study of 8,436 beneficiaries who received both a diagnosis of headache and a prescription for a migraine-specific abortive medication over a two year time period from 1 October 2002 to 30 September 2004. Patients were categorized by exposure status to daily migraine prevention. New users (N = 1,144) were compared to subjects receiving acute headache treatment alone (N = 2,618) during 18 months of follow-up. A series of regression and matching estimators modeled the effect of prevention on ambulatory health care utilization while controlling for patient characteristics selected from Andersen's Behavioral Model of Health Care Utilization.

The study results showed that exposure to daily migraine prevention influenced ambulatory health care utilization in the Military Health System. Treatment with prevention resulted in lower rates of utilization relative to what new users of prevention would have consumed in the absence of treatment. Reductions in post-treatment spending observed among new users were primarily driven by declines in the use of non-emergent care services.

The results suggest that additional economic benefits could be realized by increasing the appropriate use of daily migraine prevention. Health care providers must play an important part in reaching this goal by targeting those individuals most likely to derive a benefit from treatment. Health policies that successfully identify untreated candidates for daily migraine prevention and encourage open discussions between providers and patients about individual patient preferences as well as the benefits and risks of prevention should be considered.

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Chapter 1

INTRODUCTION

Migraine is a common and disabling neurological disorder with substantial variation in the frequency, severity, and duration of headaches (Goadsby, Lipton, & Ferrari, 2002). Over the last decade, enhanced health technologies have improved providers' ability to treat patients who suffer from migraines. One major pharmacologic development was the identification of effective medicinal compounds for migraine prevention. Medications taken for this purpose are consumed daily regardless of headache status in an effort to reduce the frequency and severity of migraines. While the safety and efficacy of medication for migraine prevention has been established, the impact migraine prevention on health care resource consumption is not clear. A more detailed understanding of the economic outcomes associated with migraine prevention will allow providers to make more efficient decisions, improve patient outcomes, and reduce health care costs.

The principal aim of this dissertation was defined as follows:

- To determine if exposure to daily migraine prevention effects ambulatory health care utilization including costs of prescription drugs, non-emergent medical care, and emergency room care in comparison to acute migraine treatment alone.

The principal aim is compatible with a recommendation made by the American Academy of Neurology (AAN) to conduct research that will "improve current understanding of the acceptability, long-term use and effectiveness of specific preventive therapies and preventive therapies in general" (Ramadan, Silberstein, Freitag, Gilbert, & Frishberg, 2000). The long term goal of this research is to enhance the well-being of patients being treated with pharmacotherapy for migraine. The results strengthen public health in the Military Health System through an improved understanding of headache management and will diminish the disability associated with migraine headache disorders.

Looking Ahead

Chapter Two begins with a general review of migraine. Emphasis is placed on describing the burden (e.g., disability and economic impacts) of illness and reviewing the role of prevention in the management of migraine. Furthermore, a testable linkage between daily migraine prevention and health care resource utilization is proposed. The conceptual framework for this study introduced in Chapter Three defines and explains the theoretical aspects guiding both the design and implementation of the dissertation. This section includes a formal discussion of the theoretical aspects of outcomes research and introduces the behavioral model of health care utilization that provided a framework for selection of study explanatory variables. The treatment evaluation problem

commonly encountered during outcomes research also is discussed including descriptions of general estimation strategies and the corresponding assumptions required to the solve the evaluation problem.

Chapter Four describes various aspects of the study design and makes clear the hypotheses that will be tested during the analysis. In addition, the quantitative approach to treatment evaluation that was introduced during the proceeding chapter is developed further. The results of the analysis are reported in Chapter Five and Chapter Six offers a discussion of the study results including the implications, limitations, and need for future research in this area.

Chapter 2

REVIEW OF THE LITERATURE

a. Current Understanding of Migraine

Migraine is a widespread and disabling neurological disorder, manifested by bouts of severe headache that can include the presence of an aura (Goadsby et al., 2002). The disease has a long history with a great deal of interest centered on the etiology of migraine and the evolution of treatment. One of the earliest known references comes from a historical Mesopotamian text dated around 3000 B.C. which described characteristics of a headache. Garrison's History of Neurology (as cited in Rapoport & Edmeads, 2000) provided the following excerpt from the Mesopotamian text:

> "Headache roams the desert, blowing like the wind. Flashing like lightning it is loosed above and below. It cuts off like a reed him who fears not his god… This man it has struck, and like one sick of heart, he staggers; like one bereft of reason, he is broken."

The type of headache described is impossible to determine with absolute certainty. However, several characteristics from the passage closely resemble features of migraine. The extreme pain and visual components are both strongly suggestive of the disease. Regardless, a precise diagnosis during this period

was unnecessary because of a generally held belief that headache occurred secondary to a supernatural phenomenon (Rapoport & Edmeads, 2000).

In modern-day medicine, migraine continues to be a formidable disorder to diagnose because of its subjective features. The formal diagnostic criteria established by the International Headache Society (IHS) are summarized in Table 2.1. A diagnosis for migraine headache without aura requires that a person must have experienced at least five headaches that met each criterion listed in Table 2.1 (Headache Classification Subcommittee of the International Headache Society, 2004). The diagnostic criteria are useful because they allow for differentiation between migraine and other types of primary headache disorder such as tension-type or cluster headache.

TABLE 2.1. Diagnostic Criteria for Migraine Headache (without aura)

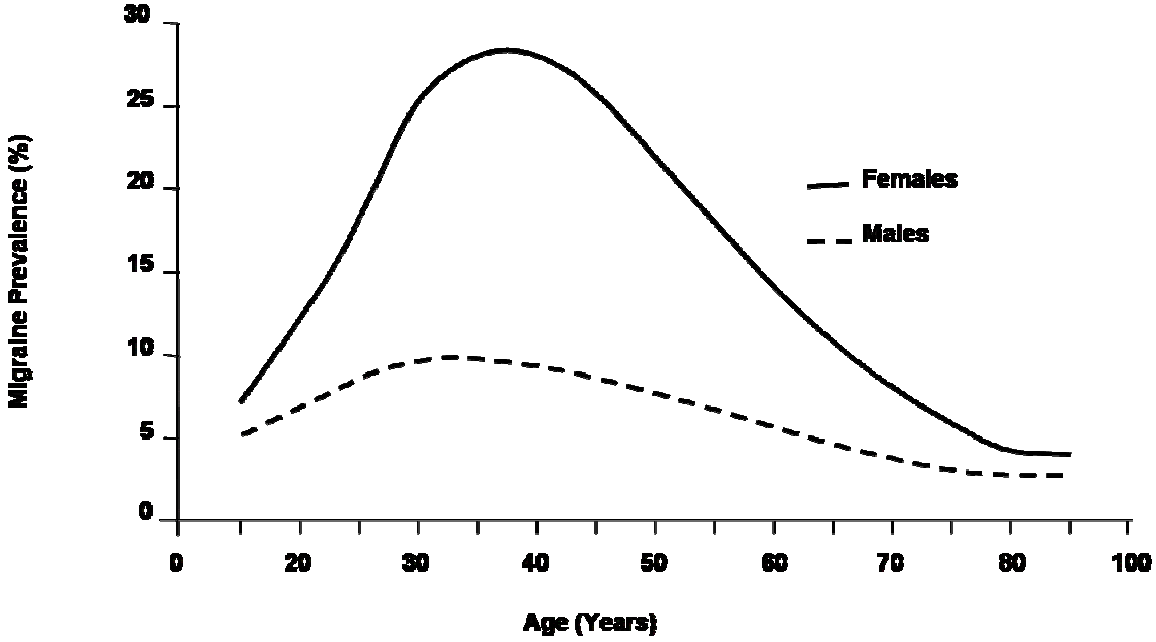
Diagnostic Criteria
Headache attack lasting 4-72 hours (untreated or unsuccessfully treated)
Headache had two of the following characteristics:
Unilateral location
Pulsating quality
Moderate or sever pain intensity
Limits routine physical activity
During headache at least one of the following:
Nausea and/or vomiting
Photophobia and phonophobia

Note. Adapted from Headache Classification Subcommittee of the International Headache Society. (2004). The international classification of headache disorders: 2nd edition. *Cephalalgia, 24*(Suppl 1), 9-160.

The distribution of the disease in the general U.S. population has been studied extensively. The most rigorous disease prevalence estimates come from the American Migraine Study II (Lipton, Scher et al., 2002), a mailed survey of 20,000 U.S. households that was designed to evaluate the presence and severity of migraine headache. The survey included a self-administered headache questionnaire that assigned migraine diagnoses based on IHS criteria (Table 2.1) and was validated in a sample of headache sufferers demonstrating an ability to differentiate between migraine headaches and other types of primary headache disorders.

The results from the American Migraine Study II reported a one year prevalence estimate of 12.6% indicating that 28 million adults in the United States suffer from regular migraines (Lipton, Scher et al., 2002). The disease was three times more common in women than men (18.6% vs. 6.5%). Figure 2.1 illustrates the age adjusted one year prevalence estimates stratified by gender. It suggests that similar prevalence rates occur between boys and girls prior to puberty. After puberty, however, disease prevalence rises more rapidly among women than men. Regardless of gender, peak prevalence occurs during, arguably the most productive years of life contributing to the significant disability associated with migraine. After mid-life, disease prevalence begins to decline. Nonetheless, migraine remains a life-long condition for many people.

FIGURE 2.1. Age and Gender Adjusted One Year Prevalence Estimates of Migraine in the United States

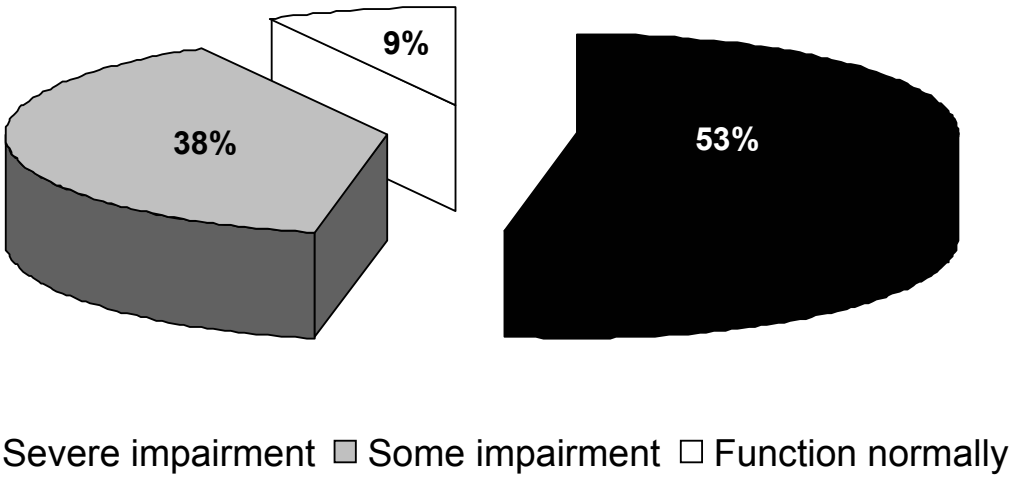


Note. Adapted from Lipton, R. B., Stewart, W. F., Diamond, S., & Reed, M. (2001). Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache, 41*(7), 646-657.

Another noteworthy aspect of the disease is the corresponding disability among those individuals who suffer from migraine. Figure 2.2 summarizes the results of a survey from a representative sample of the U.S. population designed to measure migraine-related disability. More than 90% of respondents indicated that migraine headaches were associated with some degree of functional limitation. Of greater concern, 53% of respondents reported that their migraine headaches resulted in severe functional limitations or required bed rest. Due to

the frequent disability associated with migraines, the illness was recently added to the World Health Organization study, Global Burden of Disease 2000. During the analysis, migraine was recognized as the 19th leading cause of total years lived in disability among all diseases causing disability world-wide (Leonardi, Steiner, Scher, & Lipton, 2005). As expected, migraine disproportionately affected women where it ranked 9th among global causes of years lived in disability.

FIGURE 2.2. Measure of Self-Reported Disability among a National Sample of Migraine Headache Sufferers



Note. Adapted from Lipton, R. B., Stewart, W. F., Diamond, S., & Reed, M. (2001). Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache, 41*(7), 646-657.

An exhaustive study on the impact of migraine headaches within the Military Health System (MHS) has not been published to date. However, there are several reports that suggest migraines could pose a significant problem for the MHS. Some of the earliest evidence on this topic was published in 1969 where headaches were identified as a leading cause of sick call visits encountered in the Navy (Martin, 1969). Since then, migraine headaches have been recognized as a frequent cause of permanent flying disqualifications among United States Air Force pilots and navigators (McCrary & Van Syoc, 2002).

Similarly, a recent analysis of medical conditions resulting in limited individual duty assignments of United States Navy personnel between 1998 – 2001 documented disorders of the central nervous system as the fourth most common cause of disability (Bohnker, Telfair, McGinnis, Malakooti, & Sack, 2003). The finding placed neurological disorders ahead of circulatory, respiratory, and endocrine diagnoses supporting the well documented functional limitations associated with these diseases. Also, migraines have been implicated as a commonly confronted illness in active duty troops during military operations (Bove & Oxler, 1995; Gomez, 1992) and even the use of everyday military equipment has been identified as a trigger for migraines (Cho, Clark, & Rupert, 1995). Taken together, the evidence suggests that migraines pose a real threat to the MHS, affecting individual productivity and availability of our active duty force.

Recent scientific advancements have improved providers' ability to effectively manage this condition (Goadsby et al., 2004). Despite such progress, research suggests migraineurs are commonly misdiagnosed and receive sub-optimal treatment (Lipton, Cady, Stewart, Wilks, & Hall, 2002; Lipton, Diamond, Reed, Diamond, & Stewart, 2001). The remainder of this chapter describes the current literature on the economic impact of migraine, the function of prevention in disease management, and proposes a testable linkage between preventive treatment and health care resource utilization.

b. Economic Impact and Resource Utilization Associated with Migraine

The National Center for Health Statistics has estimated that migraines account for 3.5 million ambulatory visits annually, making it the most common outpatient disorder of the central nervous system (Schappert, 1997). Despite the large number of patients suffering from migraine, many people go untreated and do not seek care for the illness or self-manage the condition with over-the-counter products (Lipton, Stewart, Celentano, & Reed, 1992; Lipton, Stewart, & Simon, 1998).

Individuals who are treated utilize a substantial amount of health care resources. Clouse and Osterhaus (1994) conducted an analysis of claims comparing total health service use in a group of patients with a diagnosis of migraine to a group without a migraine diagnosis. The comparison group was matched with the migraine group on age, gender, and enrollment status. The

results showed that migraineurs accounted for twice the number of medical claims, 2.5 times more pharmacy claims, and 6 times more costly diagnostic procedures than comparatively similar patients without migraines (Clouse & Osterhaus).

Moreover, excessive use of migraine-specific abortive medications has been linked to the occurrence of rebound or drug-induced headaches. For example, a population-based study of headache patients recruited through community pharmacies were surveyed on utilization patterns of migraine-specific abortive medications (MSAM) over a 27 month period (Gaist, Hallas, Sindrup, & Gram, 1996; Gaist, Tsiropoulos et al., 1998). In combination with migraine registry data, the authors found that the top 1% of all MSAM users was responsible for greater than 20% of abortive medication use during the study period. They concluded that rebound headaches from over use of MSAM were, in part, responsible for excessive use observed among the study population. If daily migraine prevention could successful reduce the use of these abortive medications, it might also lessen the risk of this rebound phenomenon.

The most frequently cited estimate of the economic costs for treatment of migraine in the United States was published in 1999. In this article Hu, Markson, Lipton, Stewart and Berger (1999) estimated the frequency and cost of health care service use stratified by age and gender using 1994 data from MEDSTAT's MarketScan database. The charges incurred for migraine related visits served as the inputs to estimate the national rate of health service utilization and its

corresponding cost. The results were then generalized to the United States population using prevalence data from the American Migraine Study. The findings suggested that direct costs of migraine accounted for $1.2 billion annually.

The majority of migraine headache costs accrue from physician services, emergency room visits, and prescription drug use (Gibbs, Fleischer, Feldman, Sam, & O'Donovan, 2003; Ferrari, 1998). It should also be noted that the findings from Hu et al. (1999) most likely underestimate the direct costs of migraine-related care in the United States today. For instance, the U.S. market for sumatriptan (Imitrex®), one of seven triptans currently available for the symptomatic relief of migraine, was reported at 1.2 billion dollars in 2004 (NDCHealth, 2004). Excluding the effect of inflation, the cost of just one prescription medication used primarily for the treatment of migraine exceeded the estimated total cost of all migraine-related care provided in the U.S. just five years earlier. This would suggest that more work is needed to better estimate the total cost of direct care attributable to migraine. Still, it is clear that a significant amount of health resources are consumed in the treatment of this disease every year.

Although not directly measured during this analysis, indirect costs also play a substantial role in the disease burden (Burton, Conti, Chen, Schultz, & Edington, 2002; Lipton, Stewart, & von Korff, 1997; Stang & Osterhaus 1993; Stewart, Ricci, Chee, Morganstein, & Lipton, 2003). Several studies show that

indirect costs far exceed the direct medical costs associated with migraine (Burton, Conti et al.; Lipton, Stewart et al.; Stewart, Ricci et al.). The major sources of indirect costs have been attributed to work-days lost and reduced productivity while at work (Lipton, Stewart et al.; Osterhaus, Gutterman, & Plachetka, 1992; Stewart, Shechter, & Lipton, 1994). In fact, the estimated impact of indirect costs to American employers in 1999 was $13 billion dollars with $8 billion dollars due to missed work-days alone (Hu et al., 1999). As a result, it should be a priority to manage the condition in a safe and cost-effective manner.

c. Role of Prevention in the Management of Migraine

Over the last decade, numerous advances have improved providers' ability to treat patients who suffer from migraines. One major breakthrough was the expansion of effective choices for daily migraine prevention. Interestingly, the exact mechanism of action associated with daily migraine prevention is unknown (Loder & Biondi, 2005). The effect of reducing the severity or frequency of migraine headaches was usually discovered by chance when preventive medications were prescribed for other purposes. Limited insight into the pathophysiology of the disease has led to numerous reports of products with anecdotal evidence supporting their use in the prevention of migraine.

As a result, the American Academy of Neurology developed evidenced-based guidelines to assist providers in the identification of patients who should

be considered candidates for daily migraine prevention. The final report promoted the use of daily prevention in migraine patients who met one or more of the following criteria listed in Table 2.2 (Ramadan et al., 2000).

TABLE 2.2. Indications for Treatment with Daily Migraine Prevention by the International Headache Consortium

Indications for Migraine Prevention
Recurring migraines that, in the patients' opinion, significantly interfere with daily routines, despite acute treatment
Frequent headaches
Contraindication to, failure of, or overuse of acute therapies
Adverse events with acute therapies
Cost of both acute and preventive therapies
Patient preference
Presence of uncommon migraine conditions

Note. Adapted from Headache Classification Subcommittee of the International Headache Society. (2004). The international classification of headache disorders (2nd ed.). *Cephalalgia, 24*, 9-160.

In addition, the guideline reviewed the existing evidence for medications thought to be effective in the prevention of migraines. In total, the authors reviewed 283 controlled trials of daily migraine prevention focusing on the clinical efficacy and adverse event profile of each medication. (Ramadan et al., 2000) The results categorized each treatment choice into one of five groups. The groups are described as follows (Ramadan et al., 2000):

- Group One: medication in this category possess “medium to high efficacy, good strength of evidence, and mild-to-moderate side effects” and should be considered first line for prevention of migraine
- Group Two: medication in this category possess “lower efficacy (i.e., smaller number of studies or evidence suggesting modest improvement), mild-to-moderate side effects” and are still widely used for prevention
- Group Three: “medication use based on expert opinion alone and is not supported by randomized controlled trials”
- Group Four: “medication with proven efficacy but frequent or severe side effects or difficult management issues”
- Group Five: denotes medication with “no evidence indicating efficacy over placebo” and should be avoided in migraine prevention

This dissertation was limited to an analysis of medications classified as “group one” or “group two” because these products provided the best clinical option for daily migraine prevention. Group designations three through five were excluded because there was no scientific evidence that they were effective for migraine prevention. Furthermore, if they had been included as a comparison group it would have limited membership in other study cohorts because of previous exposure to prevention during the pre-treatment interval. As a result, the study only evaluated medications in the first two groups to focus on effective preventive products and maximize the precision of each study result.

TABLE 2.3. Preventive Therapies for Migraine Classified by American Academy of Neurology

Group One	*Group Two*	*Group Three*	*Group Four*	*Group Five*
amitriptyline	atenolol	cyproheptadine	methysergide	carbamazepine
divalproex	fluoxetine	bupropion		clomipramine
propranolol	gabapentin	diltiazem		clonazepam
timolol	guanfacine	doxepin		clonidine
topiramate†	magnesium	fluvoxamine		indomethacin
	metoprolol	imipramine		nicardipine
	nadolol	mirtazepine		nifedipine
	nimodipine	nortriptyline		pindolol
	riboflavin	paroxetine		
	verapamil	proptriptyline		
		sertraline		
		tiagabine		
		trazodone		
		venlafaxine		

Note. Adapted from Ramadan, N. M., Silberstein, S. D., Freitag, F. G., Gilbert, T. T., & Frishberg, B. M. (2000). Evidenced-based guidelines for migraine headache in the primary care setting: Pharmacological management for prevention of migraine. † This product was recognized as group three when the guidelines were released in 2000. Since that time, topiramate received an FDA indication for migraine prevention and is now considered a first-line option for headache prevention.

Medications recognized by the American Academy of Neurology as effective for daily migraine prevention are listed above in Table 2.3. Used correctly, an achievable goal should allow two-thirds of patients receiving daily migraine prevention to experience a fifty percent reduction in frequency of headaches (Cady & Dodick, 2002; Diener, Kaube, & Limmroth, 1998; Goadsby et al., 2002). While this goal still allows room for improvement, the reduction in headaches may exert a significant influence on direct medical costs associated

with the management of migraines. In the next section, the evidence for the effect of daily migraine prevention on an individual's subsequent ambulatory medical costs is reviewed.

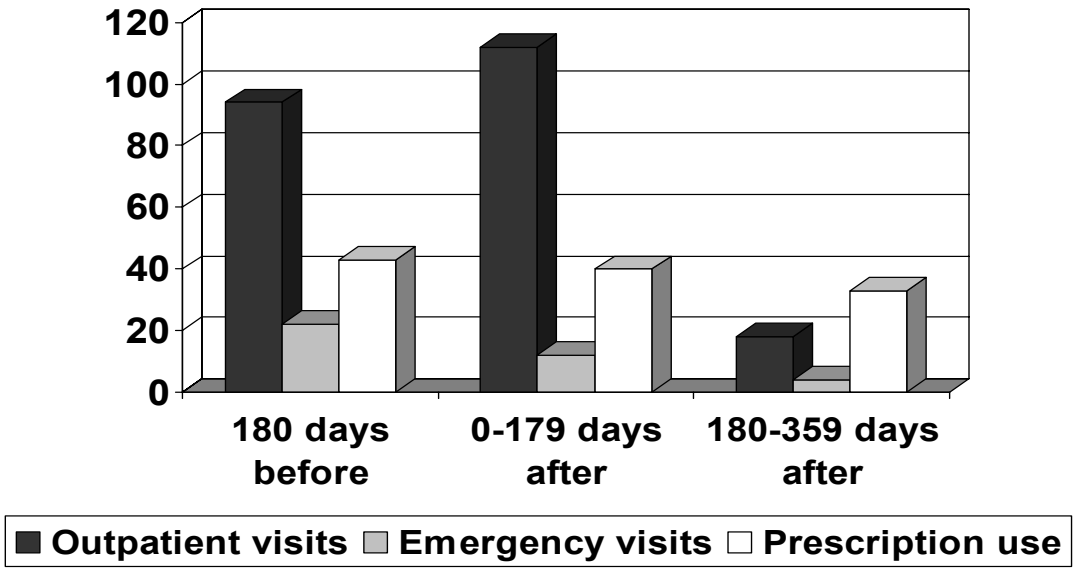
d. Evidence of a Connection between Prevention and Resource Use

To date, two published studies have examined the relationship between migraine prevention and resource utilization. Silberstein, Winner and Chmiel (2003) conducted an analysis of claims using a one group pre-test post-test design of patients who initiated daily migraine prevention. The authors compared several measures of utilization over two consecutive 180 day periods following initiation of daily migraine prevention to the amount of resource use during the 180 day period leading up to initiation of migraine prevention. The study findings are summarized in Figure 2.3. The authors concluded that the addition of a preventive medication to an individual's migraine treatment reduced utilization of abortive prescription medications, physician visits and emergency room visits which resulted in an overall cost-savings.

However, the results of this study were criticized because the analysis lacked a control group making it impossible to rule out common alternative explanations for the study findings such as regression to the mean. In addition, the study did not account for the costs of daily migraine prevention before concluding that treatment resulted in cost savings. Finally, the authors did not consider any other patient characteristics that may have influenced the observed

relationship between daily migraine prevention and migraine-related costs leaving open a strong possibility of spurious association (Adelman, Adelman, Von Seggern, & Teague, 2003). Although the authors concluded that initiation of daily migraine prevention led to cost savings through decreases in resource utilization, problems with the study design left the question open to debate.

FIGURE 2.3. Patterns of Ambulatory Health Care Utilization among Individuals Beginning Daily Migraine Prevention

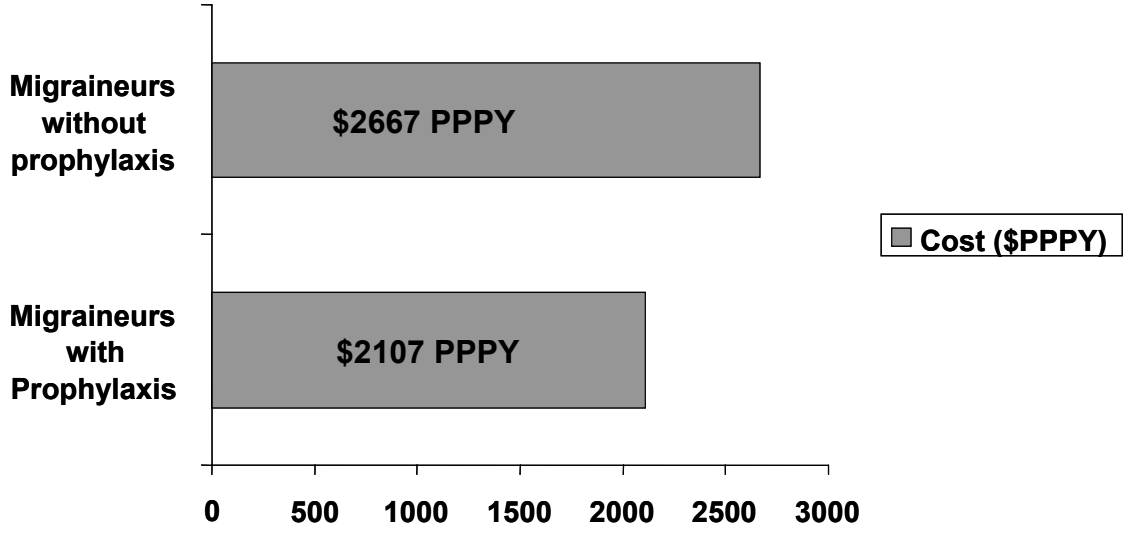


Note. Adapted from Silberstein, M. D., Winner, P. K., & Chmiel, J. J. (2003). Migraine preventive medication reduces resource utilization. *Headache, 43*(3), 171-178.

More recently, Etemead, Yang, Globe, Barlev, and Johnson (2005) examined the costs of migraine-related health care services in moderate-to-severe migraine patients treated with daily migraine prevention compared to

migraine patients who were not treated. The primary study result is depicted in Figure 2.5. The figure shows that prevention was associated with a 21% reduction in costs yielding an average decrease of $560 (1998 dollars) per patient per year (PPPY) in migraine-related costs. This analysis agreed with the previous article that suggested treatment with daily migraine prevention led to cost-savings for the health plan.

FIGURE 2.4. Comparison of Migraine-Related Health Costs among Patients



Note. PPPY = per person per year. Adapted from Etemead, L. R., Yang, W., Globe, D., Barlev, A., & Johnson, K. A. (2005). Costs and utilization of triptan users who receive drug prophylaxis for migraine versus triptan users who do not receive drug prophylaxis. *JMCP, 11*(2), 137-144.

Yet, several limitations in the Etemead et al. (2005) study should be considered before concluding that daily migraine prevention does truly result in

cost savings. For example, the article had restrictive study inclusion criteria limiting generalizeability. Also, the authors did not attempt to adjust for the endogenous group assignment in their analysis. Because exposure to daily migraine prevention was not randomly assigned, it is possible that unobserved variables correlated with both treatment assignment and health outcomes are responsible for the study effect. Moreover, they had a very small number of control variables limiting their ability to adjust for observed confounders.

While all these limitations are problematic, in an appropriate context they could be tolerated and should not be considered fatal flaws. The limitation that should preclude readers from making inferences about the study results came about during the authors' selection of the comparison group. In the Etemead et al. (2005) paper, the comparison group (i.e., migraineurs without prophylaxis) was defined as "individuals that did not receive preventive treatment but were required to possess 18 triptan equivalents during the first 6 months following the index-migraine related claim." Essentially, this required the comparison group to consist only of those individuals who were the highest users of triptan-based medications in the post-treatment period. The authors' logic was that these individuals would have been the most likely candidates to benefit from daily migraine prevention because they used large amounts of abortive medication suggesting the occurrence of frequent migraine headaches.

On the other hand, this approach might have inadvertently spawned a serious selection problem which led to biased results. As mentioned earlier, the

study's primary outcome was total health care costs incurred during the one year follow-up period (Etemead et al., 2005). The largest component of total health care costs was pharmacy costs responsible for 88.1% of total spending. Additionally, the triptan-based pharmaceuticals were the most costly medications for the treatment of migraine. Thus, by selecting the comparison group based on the amount of triptan use during the follow-up period, the authors insured that the comparison group was comprised of only the most expensive patients during the follow-up period. So, it was not surprising that the study demonstrated a significant decline in total health care costs among individuals receiving daily migraine prevention.

This highlights one of the most important aspects of conducting an observational study; the appropriate identification of the counter-factual argument to the treatment being studied. In other words, the study must accurately define what would have happened to the treatment group in the absence of treatment. The Etemead et al. (2005) paper fails in this regard because it makes the untenable assumption that everyone in the treatment category would have been among the highest in total costs had they not receive daily migraine prevention. Based on this limitation, additional work was undertaken to reevaluate the importance of daily migraine prevention on an individual's propensity to use health care services.

e. Synthesis of Literature Review

In summary, the review of published literature would suggest that migraine patients are frequent and expensive users of the health care system. Furthermore, the strategy of preventing migraines in individuals with moderate-to-severe disease has been shown to be clinically effective and might also be useful in improving economic outcomes in this patient population. Still, shortcomings of previous research have limited our understanding of the economic impacts associated with daily migraine prevention. This conclusion underscores the need for additional research into the effect of migraine prevention on clinical and economic outcomes. The results will extend the existing knowledge on daily migraine prevention and address the limitations of previous work.

Chapter 3

CONCEPTUAL FRAMEWORK

a. Overview of Conceptual Framework

The purpose of this chapter is to introduce the reader to each component of the conceptual framework and identify a common thread that binds each component to the study aims introduced at the beginning of the dissertation. The development of the conceptual framework relied on several areas of previous research and was designed to help strengthen the causal argument for the study conclusions. Once complete, the conceptual framework should complement the rest of the study by establishing the theoretical aspects that guided much of the decision-making throughout the design and implementation of the analysis.

The next section of this chapter begins with an introduction and discussion of the Economic Clinical and Humanistic Outcomes model (Kozma, Reeder, & Schulz, 1993). This traditional model of outcomes research provided the theoretical framework for the study design and inspired the selection of the study outcome measures. Next, a review of the Behavioral Model of Health Care Utilization is described to establish the criteria used for selection of the study explanatory variables (Andersen, 1968; Andersen & Newman, 1972). The chapter concludes with a discussion of the treatment evaluation problem that

results in scientific inquiry with an emphasis on the analysis of data derived under other than experimental conditions. The importance of this concept should be clear to clarify the assumptions underlying the estimation of treatment effects derived from observational data.

b. Economic Clinical and Humanistic Outcome (ECHO) Model

The ECHO model was formally described by Kozma et al. in 1993. It was designed to aid researchers interested in examining causal relationships between pharmaceutical treatments and health outcomes. Moreover, the ECHO model suggested several improvements to the traditional medical decision-making model which was primarily focused on clinical indicators and clinical outcomes of disease (Del Mar et al., 2006).

As the name implies, the ECHO model incorporated economic (e.g., direct cost of treatment) and humanistic (e.g., quality-of-life) components in addition to the clinical outcomes of the traditional medical decision-making model. The authors acknowledged that these components had been implicitly considered in earlier research that examined non-clinical outcomes of medical interventions. However, this paper was one of the first to formally define the components and place them within a broader framework designed to assess the value of pharmaceutical treatments.

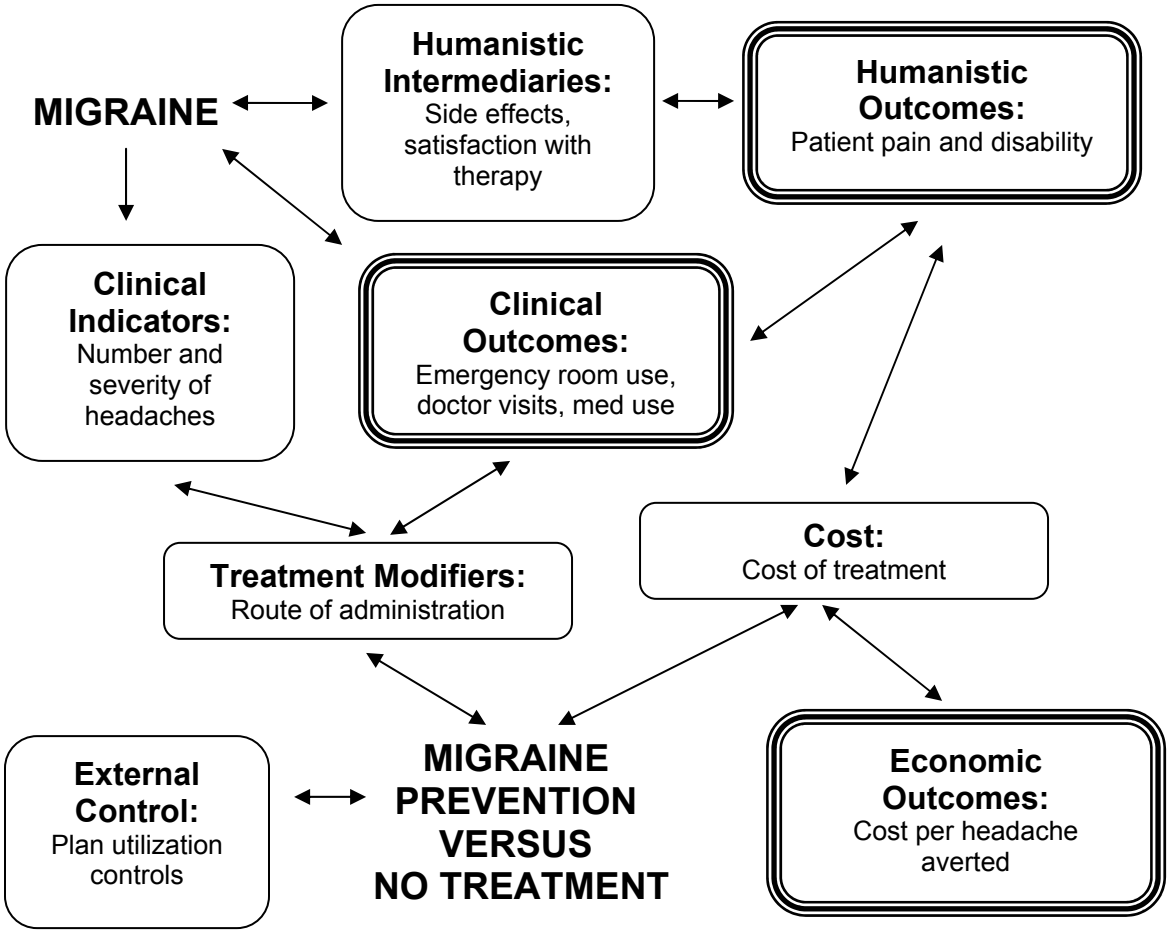
Consequently, this model served as an ideal theoretical framework for identification and collection of outcomes important in evaluation of migraine

prevention. Figure 3.1 is an adaptation of the ECHO model applied to migraine. The model illustrates the comparison of the study defined treatment alternatives (i.e., exposure to daily migraine prevention versus acute treatment only) and identifies distinct outcomes with examples at each point that could be considered when assigning a value to daily migraine prevention.

The ECHO model emphasized the large number of potential outcomes that could be considered when evaluating pharmaceutical treatments. By placing daily migraine prevention into this context, it clarified the existing gaps in our knowledge. For example, clinical indicators have been studied in detail establishing the efficacy of daily migraine prevention. However, information on other important outcomes from the model were either unavailable or of limited usefulness due to methodological shortcomings in the studies that generated the results.

Due to the wide-ranging design of the model, it was unlikely that one study could successfully capture information on all relevant outcomes for daily migraine prevention. Instead, the value of this treatment will likely be determined on an ongoing basis from a variety of studies that include diverse populations and measure various outcomes. Following the ECHO model framework, this thesis contributed to the existing evidence on the value of daily migraine prevention. The emphasis of this evaluation centered on several important clinical and the cost outcomes associated with migraine prevention and are discussed in greater detail during Chapter Four.

FIGURE 3.1. Application of the ECHO Model to Migraine and Preventive Treatment



Note. Adapted from Kozma, C.M., Reeder, C.E., & Schulz, R.M. (1993). Economic, clinical, and humanistic outcomes: A planning model for pharmacoeconomic research. *Clinical Therapeutics, 15*(6), 1121-1132.

c. Behavioral Model of Health Care Utilization

Another important aspect of the conceptual framework was the development of a theoretical process to rule out potential alternative explanations

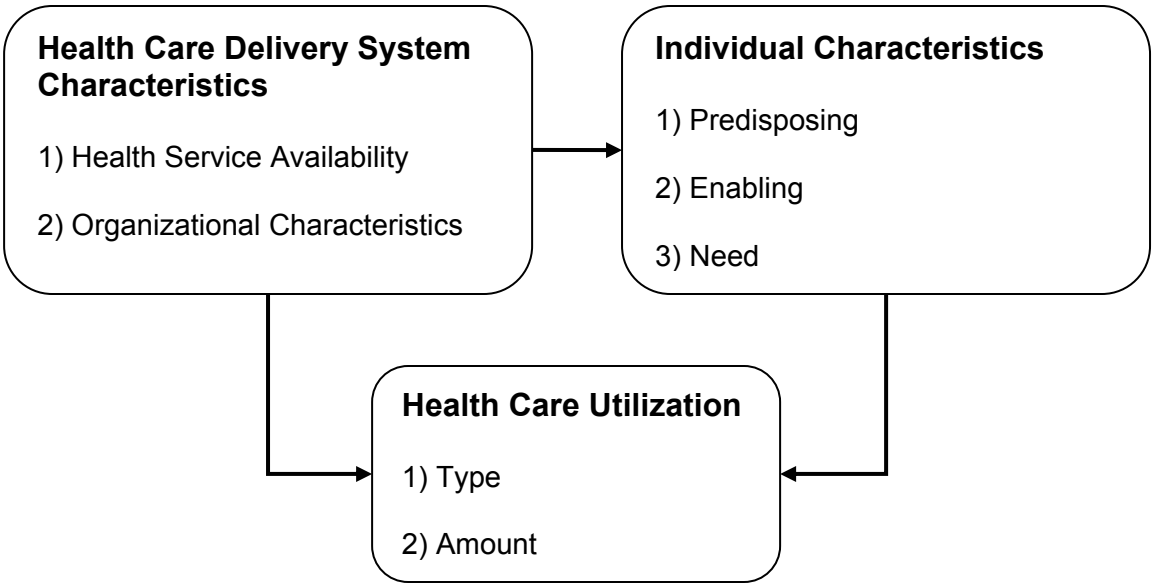
for observed associations between daily migraine prevention and use of health care services among individuals in the Military Health System. This required the development of a conceptual model that adequately explained the determinants of health care utilization in the study population. Due to extensive theoretical development and practical evidence, the Behavioral Model of Health Care Utilization was selected and adapted for this purpose. This section provides a brief review of both the original conceptual model and the adapted model used during this study.

The Behavioral Model of Health Care Utilization was originally proposed by Ronald Andersen in 1968 to explain access to health care (Andersen, 1968, 1995; Andersen & Newman, 1972). The model proposed three major categories of individual characteristics that predicted or explained an individual's use of health services. The first category was labeled as predisposing characteristics and included variables associated with a proclivity for health service use (e.g., age or gender). The next category was designated as enabling characteristics which consisted of variables thought to impede the use of health care services (e.g., the absence of health insurance). The final category was labeled as need characteristics and included both an individual's perceived need and provider's clinical assessment of a patient's need for additional health care.

The model has since been expanded to include other factors associated with health care service use (Aday, 1993). The updates have primarily incorporated characteristics of the health care delivery system. This expansion

to the model acknowledged the importance of service availability at the facility where a patient receives health care. For example, the availability of neurology services at a particular facility might increase the likelihood that a patient with migraine would be referred to a neurologist for additional care. Furthermore, the updated model integrated organizational characteristics of the health care delivery system when explaining an individual's health service use. Both factors had important implications in this context and the model was improved by their consideration. The expanded model is depicted graphically in Figure 3.2.

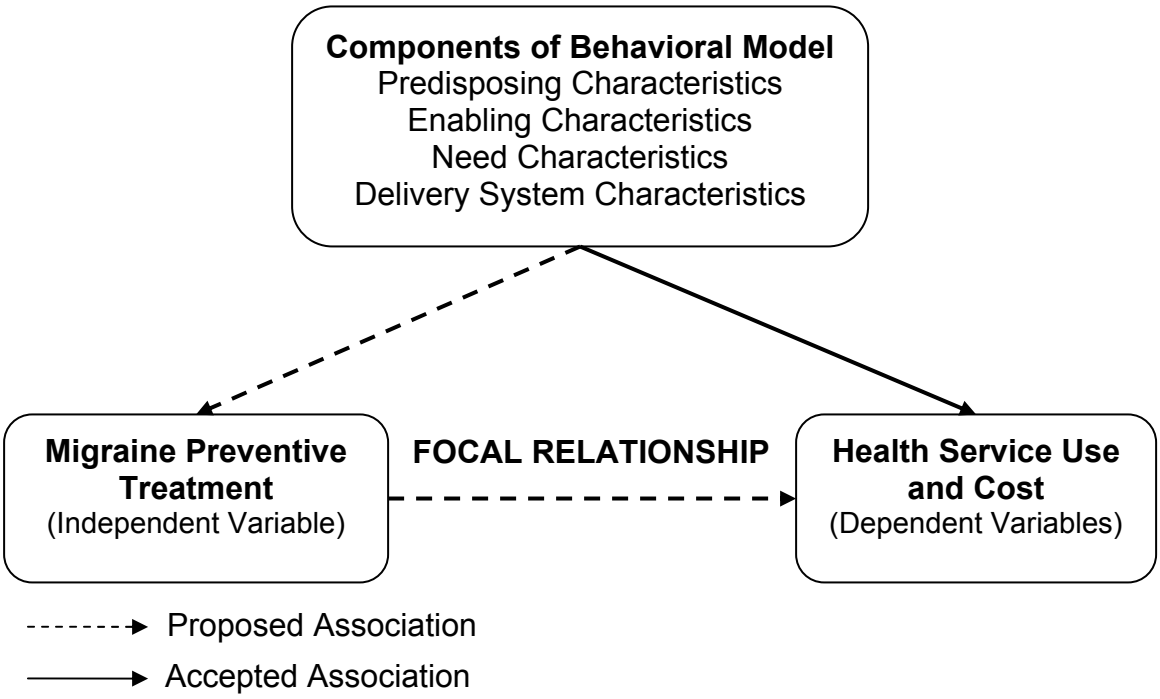
FIGURE 3.2. The Expanded Behavioral Model of Health Care Utilization



Note. Adapted from Aday, L. A. (1993). Indicators and predictors of health services utilization. In S. J. Williams and P. R. Torrens (Eds.), *Introduction to health services* (pp. 46-70). Albany, NY: Delmar.

The current study was not developed to evaluate the utility of the Behavioral Model for Health Care Utilization among patients with migraine in the Military Health System (MHS). Instead, the model was applied to the focal relationship of the dissertation (depicted in Figure 3.3) to help rule out other sources of variation and strengthen the causal argument for the focal relationship represented by a dotted arrow (Aneshensel, 2002). In this capacity, the Behavioral Model of Health Care Utilization guided the identification and selection of possible alternative explanations for the focal relationship.

FIGURE 3.3. Application of the Adapted Behavioral Model for Health Care Utilization to the Focal Relationship



The theory suggested that the components of the behavioral model in Figure 3.3 were associated with health care service use. This known association was represented by a solid arrow. If the same components of the behavioral model were also associated with the decision to begin daily migraine prevention, they would become potential confounders of the focal relationship and should be accounted for during the research design and analysis. It seemed logical that many of the factors affecting an individual's use of health care services could also influence the decision to begin treatment with daily migraine prevention. For example, disease severity would be a strong predictor of both health service use and the probability of receiving migraine prevention. This potential association was represented by a dotted arrow in Figure 3.3.

Use of the behavioral model supplied a robust framework for theory based variable selection and provided a useful guide to rule out alternative explanations for the study focal relationship. During the analysis, the final measure of effect for each hypothesis was conditioned on the observed components of the behavioral model to build a causal argument for the study results. However, the administrative database did not measure every component of the behavioral model. This missing data and the observational study design limited the possibility that every conceivable explanation for the focal relationship could be ruled out. Thus, a lingering possibility remained that an unobserved phenomenon was responsible for the observed study results.

This is a common problem in observational studies (i.e., studies using non-experimental data) of administrative data. The next section discusses a framework for understanding why this problem occurs in studies of administrative data. Also, it identifies the assumptions required for unbiased estimation and causal inference from observational study designs.

d. Difficulty of Treatment Evaluation with Observational Data

The following perspective on the evaluation problem and its solution was derived predominately from the economics literature which has expanded through ongoing efforts to evaluate the effect of labor training programs with observational data. This literature developed because of the inherent difficulties associated with conducting true experiments with these programs. In fact, several of the methodological tools used during health outcomes studies have their roots in this domain. The remainder of the section includes a discussion of estimating treatment effects from observational data. In addition, it briefly explains several assumptions commonly used to solve the evaluation problem. Both topics were important to the conceptual framework and support the estimation strategy discussed in greater detail during Chapter Four.

Using the notation of Heckman, Ichimura and Todd (1997), imagine study subjects are in one of two potential states designated as “0” and “1” respectively. State “0” corresponded to an individual with migraine that did not receive daily migraine prevention during the study observation period and state “1” implied the

converse. If Y was the outcome of interest, then the potential outcomes for each individual is defined as Y_0 or Y_1 dependent on an individual's state. If D = 1 for individuals in state "1" and D = 0 for individuals in state "0" then an individual's actual outcome is defined as:

$$Y = DY_1 + (1-D)Y_0$$

Given this relationship between the potential outcomes, the primary measure of treatment effect is defined as $\Delta = Y_1 - Y_0$. This measure requires that both Y_1 and Y_0 are observed for each study subject. If you could observe each subject's outcome under the presence and absence of treatment, then a measure of Δ could be calculated for each person and estimating the effect of treatment would be unambiguous.

Unfortunately, the potential outcomes for each individual are impossible to determine simultaneously. As a result, the primary difficulty of estimating treatment effects with experimental and non-experimental data becomes a missing data problem (i.e., we cannot observe how treated participants would have responded in the absence of preventive treatment). The difficulty of treatment evaluation under this scenario is the creation of an appropriate counter-factual outcome (i.e., response among treated subjects in the absence of treatment). As a result, researchers are forced to replace the missing data with a series of assumptions to identify patients that are indistinguishable to the treated

subjects in every regard except on the use of the study intervention (e.g., exposure to daily migraine prevention).

The gold-standard for constructing an appropriate counter-factual outcome relies on randomized treatment assignment. Done correctly, randomization will achieve statistical independence between treatment assignment (D) and the potential outcomes (Y_0 and Y_1). Most importantly, the outcome obtained from the untreated comparison group in an experimental design would be equivalent to the counter-factual outcome discussed earlier (i.e., the outcome among treated participants in the absence of treatment). An estimate of the treatment effect could then be inferred using a simple comparison of means between the two groups. Hence, many scientists consider experimental data to be superior to data generated from other processes.

Despite the substantial benefits associated with experimental research designs and randomized treatment assignment, this approach is not a panacea for solving the evaluation problem. Several potential difficulties can occur. For example, it may be unethical to randomize a patient to no treatment if the intervention is known to be effective. Also, in an environment of limited resources, the cost of conducting an experiment may prohibit the evaluation of an otherwise important research question. Under these circumstances, non-experimental studies can be a useful alternative.

Non-experimental data is information collected in the absence of random assignment. As a result, earlier assumptions about the statistical independence

between treatment assignment and outcomes are less tenable with non-experimental data then it was with experimental design where it can be argued that group membership is exogenous. Instead of a random process generating treatment assignment, non-experimental treatment decisions are a function of both observed and unobserved characteristics at multiple levels (e.g., individual, provider, or facility level). Thus, a simple comparison of means from non-experimental data will give a biased estimate of the treatment effect because the average outcome in the untreated comparison group is not equivalent to the true counter-factual outcome.

To achieve the appropriate counter-factual outcome requires that some assumptions be made about non-experimental data. At present, the non-experimental estimator with the strongest theoretical support is instrumental variable estimation. This approach requires the user to identify a variable that has two properties. First, it must be associated with the observed treatment assignment. Second, it cannot directly affect the outcome of interest except through its influence on treatment (Newhouse & McClellan, 1998). Each variable meeting both properties is referred to as an "instrument" and the exogenous variation in the outcome explained by the instrument is used to estimate a measure of effect.

If both properties are met the measure of effect generated from instrumental variable estimation represents the average treatment effect among the subpopulation of individuals whose treatment assignment was induced by the

instrument (Newhouse & McClellan, 1998). The advantage of this approach is the theoretical ability to remove both observed and unobserved sources of bias from estimated treatment effects. Unfortunately, the data evaluated during this study lacked an obvious instrument that met both properties described above. Moreover, selection of a "weak" instrument would increase the bias of estimated treatment effects worsening the problem instrumental variable estimation is designed to fix (Staiger & Stock, 1997). Thus, an alternative non-experimental estimator – matching with sensitivity analysis – was chosen to construct the counter-factual outcome for treated subjects in this analysis and thereby strengthen the causal argument of the results.

Matching with observational data can yield an unbiased estimate of the treatment effect if the following conditions are satisfied: (1) that conditional on observed covariates, outcomes are independent of treatment assignment; and (2) that the probability of treatment lies between 0 and 1. This is generally referred to as the "strong ignorability" assumption or selection on observables (Rosenbaum & Rubin, 1983). If the assumption holds, the appropriate counter-factual argument for treated subjects has been identified and measures of the treatment effect are unbiased.

The most often cited limitation of matching is the plausibility of the assumption that selection is determined completely by observed characteristics. Given the typical information available during analysis of claims data, the validity of the assumption should rightly be viewed with some skepticism. As a result,

good observational studies will be concerned about unobserved variable bias and take steps to quantify the importance of this limitation. For example, sensitivity analyses can be employed for this purpose.

During this study, a sensitivity analysis first proposed by Rosenbaum (2002) was conducted to examine the strength of results from the matched analysis to a hypothetical unobserved covariate. Essentially, the sensitivity analysis eased the assumption of equal treatment probabilities between matched subjects. As a result, I could estimate how inferences from the matched analysis might change in the presence of unobserved variable bias.

The mixture of matching and sensitivity analysis provided an effective alternative for constructing the counter-factual argument to treated subjects with observational data. As discussed during this section, this is one of the most difficult parts of treatment evaluation with observational data. A more detailed discussion of the technical aspects of matching and sensitivity analysis estimation is discussed in Chapter 4 under statistical considerations. However, analytic strategies were introduced in conjunction with the conceptual framework to insure that readers understand the assumptions underlying the analysis. Moreover, it provided a clear rationale for selecting this approach over alternative estimation strategies.

e. Synthesis of Conceptual Framework

The purpose of this chapter was to introduce each component of the conceptual framework employed during the study. The chapter began with a description of the Economic, Clinical, and Humanistic Outcomes (ECHO) model useful when examining causal relationships between pharmaceutical treatments and health outcomes (Kozma et al., 1993). The Behavioral Model of Health Care Utilization also was discussed as a method to identify possible confounding factors for observed associations between daily migraine prevention and use of health care services (Andersen, 1968, 1995; Andersen & Newman, 1972). The chapter concluded with a discussion on treatment evaluation and observational data. The idea of potential outcomes and counterfactuals was introduced along with quantitative methods for estimating treatment effects in this setting.

In summary, the connection between the study aim and conceptual framework should be clear. Moreover, the conceptual framework should be viewed by its ability to strengthen the causal argument of the study conclusions. However, before this information is presented, a closer look at the research design and methodology used during this study is warranted.

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Chapter 4

RESEARCH DESIGN AND METHODOLOGY

a. Overview of Design

The analysis was designed as a retrospective cohort study of pharmacy and medical claims data among beneficiaries of the Military Health System (MHS). In order to achieve the study objective, the analysis examined the association between daily migraine prevention and ambulatory health care expenditures including both cross-sectional and longitudinal measurements while controlling for pre-treatment expenditures and other important covariates known to effect health care utilization. The study was conducted over a two year time frame from 1 October 2002 to 30 September 2004. The evidenced-based guidelines (discussed above) supporting the use of daily migraine prevention were published in the latter half of 2000. The study timeline was chosen because it simultaneously provided recent data on migraine treatment patterns in the MHS and allowed sufficient time for therapeutic recommendations to be adopted at clinical practice sites around the country.

An observational approach using an administrative database was appropriate and useful in this analysis for several reasons. First, a randomized controlled intervention trial was not feasible because daily migraine prevention is established, efficacious therapy. Thus, it would have been unethical to

randomize an individual to no treatment. Furthermore, the study population was more representative of a typical population of migraine sufferers which enhanced the generalizability of study results and conclusions. Also, the design examined the effect of treatment in a usual care setting that provided a more practical evaluation of daily migraine prevention. Most importantly, the proposed analysis was completed at a fraction of the cost of alternative study designs. The results generated useful information on the need for and development of future intervention trials.

b. Study Data Warehouse

The study data was collected from pharmacy and medical claims in the Military Health System (MHS) Mart (M2) database. This database stores clinical and financial information of health encounters across all MHS regions. The data is maintained by the Executive Information and Decision Support (EI/DS) program office. Stored data is designed for use as a management and reporting tool that can provide summary or detailed views of the MHS population. This analysis evaluated information from three segments of the M2 data warehouse:

Standard Ambulatory Data Record (SADR): The SADR is an electronic administrative database containing all outpatient encounters within a military run hospital or clinic. This type of care is referred to as *direct care* because it is provided by the MHS. The database included information on physician and

emergency room visits such as diagnoses codes, procedure codes, date of service, workload weights, and cost information for each encounter. Direct care services measured in this study were based on information captured from the SADR. It is important to note that SADR did not include information on care delivered outside of a military treatment facility (MTF).

Healthcare Service Records Non- Institutional (HCSR-NI): To capture health care service use outside of a Military Treatment Facility (MTF) required use of the HCSR-NI file. The need for a patient to receive treatment from outside the MTF could occur for a variety of reasons. Several common explanations include reduced MTF manpower because of support for deployed military operations or the lack of certain types of specialty care in a MTF. In these instances, the patients requiring treatment would be referred to contracted civilian providers to receive care.

In the Military Health System, this type of care is referred to as *purchased care* because it is rendered outside of a traditional military setting. Each episode of treatment provided outside of a MTF is captured in the HCSR during claims processing. The claims are submitted through the managed care support contractors (MCSCs) for payment of delivered healthcare services. The HCSR has three file types including an institutional file (i.e., hospital services), a non-institutional file (i.e., outpatient visits, physician services) and a provider file. The HCSR-NI file supplies information similar to SADR (i.e., physician visits,

emergency room visits) but includes information on purchased care only. Including data from the HCSR-NI offered a more accurate assessment of resource utilization.

Pharmacy Data Transaction Services (PDTS): The final segment of the M2 data warehouse used during the analysis was the Pharmacy Data Transaction Services (PDTS) file. This database maintains a patient medication record or profile for all DoD beneficiaries worldwide, regardless of point of service. Patients eligible for prescription services can choose to fill a prescription in a MTF, a network civilian pharmacy, or the TRICARE Mail Order Pharmacy (TMOP). In each case, if the individual uses the TRICARE benefit, the transaction is captured within the PDTS database. The recorded information includes multiple fields such as prescription issue date, product name, product strength, day supply, and amount paid. PDTS provides all study data on prescription cost and utilization for enrolled patients. The data for this analysis could not be linked to the prescribing provider.

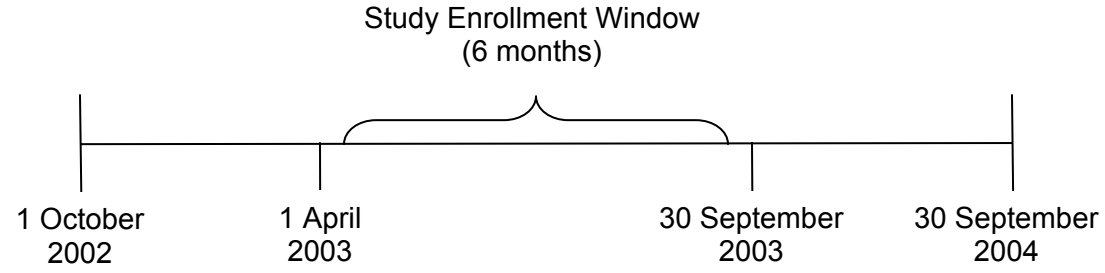
c. Data Collection

Migraine Sample Selection: The initial migraine population was selected based on documentation of headache-related pharmacy and medical encounters that occurred during the study timeline shown in Figure 4.1. The initial study population *included* patients who meet each of the following criteria:

- received a prescription for a migraine-specific abortive medication (described below) during the six month window of 1 April 2003 and 30 September 2003
- experienced an ambulatory health care encounter with an ICD-9-CM code 346.XX (migraine) during 1 October 2002 and 30 September 2004
- between 17 and 64 years of age on the index date
- eligible for care during the study period

If patients did not meet all four criteria, they were *excluded* from the initial migraine study population.

FIGURE 4.1. Timeline for Data Collection and Sample Identification



A migraine-specific abortive medication mentioned above in the inclusion criteria (1) was defined as a claim for serotonin receptor agonist (e.g. Imitrex), an ergotamine derivative (e.g., Migranal) or an isometheptene-containing product (e.g. Midrin). All migraine-specific abortive medications are summarized below in

Table 4.1 and are indicated primarily for the acute treatment of migraine headache. The abortive medications do not possess any common off-label indications which limited the possibility of misclassification bias (i.e., detection of patients who do not suffer from migraine but are receiving treatment with migraine-specific abortive medication). Furthermore, identification of patients using the inclusion criteria above was recently reported to be an effective method for claims-based recognition of migraine patients in a managed care population (Kolodner, et al., 2004).

TABLE 4.1. Drug Products Classified as Migraine-Specific Abortive Medication

Generic Name (Brand)	***Generic Name (Brand)***
almotriptan (Axert®)	isometheptene (combination product)
dihydroergotamine (D.H.E. 45®)	naratriptan (Amerge®)
dihydroergotamine (Migranal®)	rizatriptan (Maxalt®, Maxalt-MLT®)
eletriptan (Relpax®)	sumatriptan (Imitrex®)
ergotamine (single ingredient)	sumatriptan (Imitrex®)
ergotamine (combination product)	sumatriptan (Imitrex®)
frovatriptan (Frova®)	zolmitriptan (Zomig®)

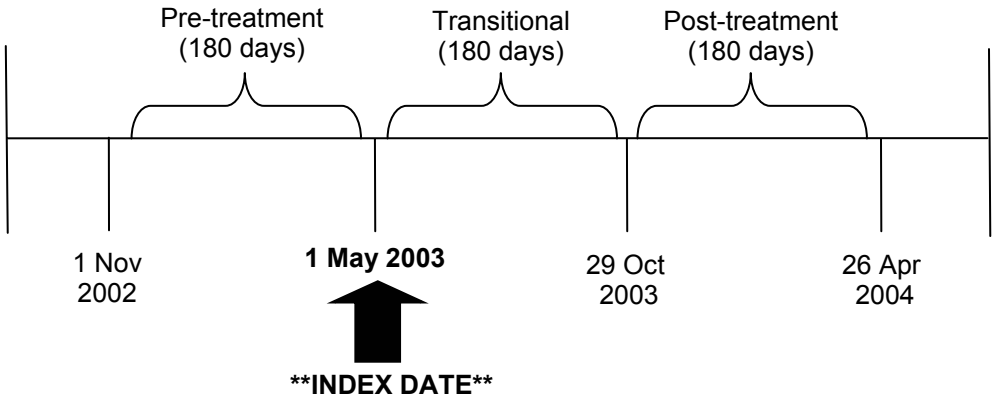
Each patient that met the inclusion criteria above was assigned an index date that corresponded to the earliest prescription claim for a migraine-specific abortive medication during the study enrollment period (1 April 2003 – 30 September 2003). Figure 4.2 shows how a hypothetical patient was enrolled for study participation. In addition, it depicts how each study interval was defined.

In this example, the patient received a prescription for migraine-specific abortive medication (MSAM) on 1 May 2003. This was the earliest prescription

for a MSAM during the 6 month study enrollment period (1 April 2003 – 30 September 2003). Accordingly, the patient was assigned an index date of 1 May 2003.

Using the patient specific index date, three 180 day intervals were defined to allow for standardized measurement of health care utilization and costs over a finite period of time. As shown in Figure 4.2, utilization and costs incurred on the index date were excluded from the 180 day intervals. This was deemed necessary to avoid inflating the outcome measures in any one interval because every subject in the study had some health care use on the index date by definition.

FIGURE 4.2. Hypothetical Example of an Individual Selected for Study Inclusion



The pre-treatment interval was defined as the 180 day period leading up to but not including the index date. The transitional interval was defined as the 180 day period immediately following the index date. It was labeled as

transitional because it was during this time that study subjects started daily migraine prevention for the purpose of defining a treated (exposed to daily migraine prevention) and untreated (acute migraine treatment without daily migraine prevention) cohort. A formal description of cohort assignment is described in a diagram on page sixty. The final 180 day period was labeled as the post-treatment interval and was defined as the 180 day period following the transitional interval. Figure 4.2 (above) shows the dates for the hypothetical example of a study subject with an index date of 1 May 2003.

d. Research Hypotheses

The study hypotheses examined the effect of daily migraine prevention on clinical and economic endpoints. The hypotheses were grouped into two categories based on the characterization of the dependent variable. The first group was *cross-sectional* because it compared post-treatment endpoints for the two study cohorts (i.e., new users and non users of prevention) over a 6 month period. The second group was *longitudinal* because it compared the change in the dependent variable from one 6 month period to the next (i.e., from the transitional period to the post-treatment period) between the two study cohorts. The diagram of study intervals described above in Figure 4.2 (above) and a formal definition of the study variables can be found on page 68 (Table 4.3).

The primary cross-sectional study hypothesis was that use of daily migraine prevention did not influence migraine-related cost of treatment incurred by the Military Health System in the post-treatment period compared to acute treatment alone. The sub hypotheses included:

H_{01} – Use of daily migraine prevention *does not influence* expenditures for medications *definitely* related to migraine in the post-treatment period compared to acute treatment alone.

H_{02} – Use of daily migraine prevention *does not influence* expenditures for medications *potentially* related to migraine in the post-treatment period compared to acute treatment alone.

H_{03} – Use of daily migraine prevention does not influence utilization of migraine-specific abortive medication in the post-treatment period compared to acute treatment alone.

H_{04} – Use of daily migraine prevention *does not influence* expenditures for migraine-related ambulatory services in the post-treatment period compared to acute treatment alone.

H_{05} – Use of daily migraine prevention *does not influence* expenditures for migraine-related emergency room services in the post-treatment period compared to acute treatment alone.

H_{06} – Use of daily migraine prevention *does not influence* total expenditures for migraine-related ambulatory services in the post-treatment period compared to acute treatment alone.

The primary longitudinal study hypothesis was that use of daily migraine prevention did not influence the change in cost of care (i.e., the difference in costs generated during the transitional and post-treatment periods) incurred by the Military Health System compared to the change in cost of care over the same time period for an untreated cohort of individuals with migraine. The sub hypotheses included:

H_{07} – Use of daily migraine prevention *does not influence* the observed change in expenditures for medications *definitely* related to the treatment of migraine compared to a similar change following acute treatment alone.

H_{08} – Use of daily migraine prevention *does not influence* the observed change in expenditures for medications *potentially* related to the treatment of migraine compared to a similar change following acute treatment alone.

H_{09} – Use of daily migraine prevention *does not influence* the change in utilization of migraine-specific abortive medication compared to a similar change following acute treatment alone.

H_{10} – Use of daily migraine prevention *does not influence* the change in expenditures for migraine-related ambulatory services compared to a similar change following acute treatment alone.

H_{11} – Use of daily migraine prevention *does not influence* the change in expenditures for migraine-related emergency services compared to a similar change following acute treatment alone.

H_{12} – Use of daily migraine prevention *does not influence* the change in <u>total</u> expenditures for migraine-related ambulatory services compared to a similar change following acute treatment alone.

Evaluation of daily migraine prevention has previously been limited to studies that compared post-treatment endpoints for migraine subjects on prevention to migraine subjects not on prevention. The endpoints from the cross-sectional analysis offered similar set of results. Thus, the cross-sectional hypotheses should allow for a direct comparison of study results to previous research.

However, a potential problem existed with cross-sectional results. As mentioned earlier, treatment could not be randomly assigned because the data was collected retrospectively. In this setting subjects were allowed to self-select into treatment groups. Based on the current indications for daily migraine prevention, individuals exposed to treatment (i.e., prevention) probably had, on average, more severe disease than those individuals who received acute treatment alone. Consequently, it would not be surprising if individuals exposed to prevention required additional health care services compared to unexposed individuals receiving acute treatment only. Such a scenario would seem to suggest that exposure to prevention led to higher costs of health care.

This conclusion would be counter-intuitive because daily migraine prevention is thought to reduce the frequency and severity of migraine

headaches. Thus, the effect of prevention was also evaluated by examining how each endpoint changed over time between the two study cohorts. The longitudinal hypotheses examined the process of change and provided an effective method to adjust for the presence of pre-existing group differences between the two study cohorts (Allison, 1990).

e. Definition of Study Variables

All study variables came directly from the queried database files or were created by manipulation of the retrieved data. Following the conceptual framework introduced in Chapter Three, the variables were categorized as a dependent, independent, or control (matching) variable. A brief description of each study variable has been summarized at the end of this section on page 67 in Table 4.4. The process of constructing study variables with formal definition for each variable is explained below.

Dependent Variables

Outpatient Prescription Drug Costs: This variable was treated as continuous and calculated for each study interval (i.e., pre-treatment, transitional, and post-treatment intervals). The measure included the costs of all prescription medications identified as either definitely or potentially related to migraine. This classification has been used previously (Lofland, Johnson, Batenhourst, & Nash,

1999) and the exact list of medications as classified in this study are summarized in Appendix A.

The cost data for this variable were extracted from PDTS using the Amount Paid field (AP_PDTS). For prescriptions filled outside of a Military Treatment Facility (MTF) (e.g., through the TRICARE Mail Order Pharmacy or the retail network), the amount paid field was calculated by summing the commercial ingredient cost, pharmacy dispensing fee, sales tax and then subtracting the patient co-pay. Prescriptions dispensed from a MTF were limited to ingredient cost and did not include a dispensing fee, sales tax or co-pays. The cost of definitely and potentially migraine related prescription medication (OP_DC) dispensed during each 180 day interval was calculated as follows:

$$OP\_DC = \sum (AP\_PDTS)_i$$

where the subscript represents the i^{th} prescription filled during the pre-treatment, transitional, and post-treatment intervals respectively. In H_{01} and H_{02}, the analysis compared OP_DC in the post-treatment interval only. For H_{07} and H_{08}, the change in outpatient prescription drug costs (ΔOP_DC) was calculated as follows:

$$\Delta OP\_DC = OP\_DC_{post\text{-}treatment} - OP\_DC_{transtional}$$

Migraine-Specific Abortive Medication Use: The use of migraine-specific abortive medication (MSAM) was designated as a continuous variable. It

reflected the total consumption of MSAM during each of the 180 day study intervals. MSAM use was measured using the Defined Daily Dose (DDD) methodology. This approach was necessary because MSAM includes a variety of medication classes and varying dosage forms. Use of DDDs allowed for standardization of medication use across all patients receiving MSAM therapy.

The concept of a DDD was originally created to compare equipotent drug doses and represents the usual dose required for treatment when taken by an adult for the primary indication (Dukes, 1993; WHO Collaborating Centre for Drug Statistics Methodology, 2004). This method has been used previously in migraine research (Gaist, Hallas et al., 1996; Gaist, Tsiropoluos et al., 1998; Rahimtoola, Buurma, Tijessen, Leufkens & Egberts, 2002, 2003). Based on the definition, a single DDD should reflect the average amount of abortive medication required to treat one migraine headache in the average adult. The definition of a DDD for each MSAM is displayed below in Table 4.2.

The calculation of DDDs for each patient required independent computation for each migraine-specific abortive medication (MSAM) a patient received. The number of DDDs for a single dosage form was calculated by multiplying the product strength and the total quantity received during each interval. This value was then divided by the corresponding DDD strength from Table 4.2 resulting in the total number of DDDs received for that particular dosage form. The process was repeated for each drug product received. Once complete, the DDDs were

then summed to determine the total amount of MSAM received during each study interval.

TABLE 4.2. Defined Daily Dose Comparison of Migraine-Specific Abortive Medications

Migraine-Specific Abortive Medication	*Dosage Form*	*Defined Daily Dose*
almotriptan (Axert®)	tablets	12.5 mg
dihydroergotamine (D.H.E. 45®)	injection	4 mg
dihydroergotamine (Migranal®)	nasal spray	1 mg
eletriptan (Relpax®)	tablets	40 mg
ergotamine (single ingredient)	any route	4 mg
ergotamine (combination product)	any route	2 mg
frovatriptan (Frova®)	tablets	2.5 mg
Isometheptene (combination product)†	capsules	5 capsules
naratriptan (Amerge®)	tablets	2.5 mg
rizatriptan (Maxalt®, Maxalt-MLT®)	tablets	10 mg
sumatriptan (Imitrex®)	tablets	50 mg
sumatriptan (Imitrex®)	nasal spray	20 mg
sumatriptan (Imitrex®)	injection	6 mg
zolmitriptan (Zomig®)	tablets	2.5 mg

Note. † Isometheptene products were not included in the Anatomical Therapeutic Classification used to assign Defined Daily Doses by the World Health Organization. Instead, Isometheptene products were assigned a conservative definition that reflected the maximum recommended amount of medication used to treat one migraine headache in one twelve hour period.

For example, if a hypothetical patient received 2 prescriptions for sumatriptan nasal spray 20 mg (each prescription containing 6 units) and also received 4 prescriptions for sumatriptan oral tablets 100 mg (each prescription containing 6 tablets), the total number of DDDs would be calculated as follows:

- DDD Nasal Spray = (20 * 12) / 20 = 12 DDDs
- DDD Oral Tablet = (100 * 24) / 50 = 48 DDDs
- Total DDD = ∑ (DDD Nasal Spray and DDD Oral Tablet) = 60 DDDs

This final estimate of migraine-specific abortive medication use measured in DDDs provided a standardized measure to make meaningful comparisons between new and non users of daily migraine prevention.

The formal definition of migraine-specific abortive medication use (MSAM_USE) dispensed during a 180 day interval was calculated as follows:

$$MSAM\_USE = \sum (DDD)_i$$

where the subscript represents the i^{th} prescription filled for a migraine-specific abortive medication during the pre-treatment, transitional, and post-treatment intervals respectively. In H_{03}, the analysis compared MSAM_USE in the post-treatment interval only. For H_{09}, the change in migraine-specific abortive medication use (ΔMSAM_USE) was calculated as follows:

$$\Delta MSAM\_USE = MSAM\_USE_{post\text{-}treatment} - MSAM\_USE_{transtional}$$

Non Emergent Medical Costs: This continuous variable captured the cost of migraine-related *non-emergent* medical care from healthcare providers. Outpatient health care encounters with a migraine diagnosis were collected over the three 180 day study intervals defined by the index date. The data was extracted from both the direct care file and the purchased care file.

In the direct care file, the cost of each encounter was derived from the Full Cost (FCR_SADR) field. This field was based on each encounter's Ambulatory Patient Group (APG) weight. APG weights were assigned based on Current Procedural Terminology Codes (American Medical Association, 2001) and ICD-9-CM codes (U.S. Public Health Service, 2001) in order to classify comparable ambulatory visits with similar resource demands for purposes of prospective payment (Information Resource Products, n.d.). To populate the Full Cost field, APG weights were multiplied by a MTF-specific cost-of-care rate per APG for the year of execution.

In TRICARE, these weights reflect both clinic and provider resource intensity. For a visit with multiple procedures and diagnoses, the aggregate APG weight was discounted by taking the sum of the largest weight and 50% of each subsequent weight assigned during the visit. This discounting more accurately reflected the resources consumed by limiting the impact of repeated services. The final amount was recorded in the Full Cost field representing the cost of each direct care visit during the study.

Reimbursement of purchased care occurred through the regional Managed Care Support Contractors (MCSCs) in conjunction with the Department of Defense TRICARE program. The MCSCs determined patient eligibility, paid the claim, and sent the results for storage in the HCSR file. To capture the cost of non-emergent health care encounters outside of a MTF, data were collected

from the populated field Amount Paid (APR_HCSR). This field represented the total dollar amount paid by the government for a particular claim.

The formal definition for the cost of migraine-related non-emergent medical care (TC_NEMC) incurred during a 180 day interval was calculated as follows:

$$TC\_NEMC = \sum (FCR\_SADR)_i + \sum (APR\_HCSR)_i$$

where the subscripts represent the i^{th} claim for migraine-related non-emergent medical care that occurred during the pre-treatment, transitional, and post-treatment intervals respectively. In H_{04}, the analysis compared TC_NEMC in the post-treatment interval only. For H_{10}, the change in total cost of migraine-related non-emergent medical care (ΔTC_NEMC) was calculated as follows:

$$\Delta TC\_NEMC = TC\_NEMC_{\text{post-treatment}} - TC\_NEMC_{\text{transtional}}$$

Emergency Room Visit Costs: The total cost of migraine-related emergency medical care (TC_EMC) was designated a continuous variable. It was calculated for every study subject in the same manner as the previous variable except that all care was rendered in an emergency room. Administrative claims from the emergency room with a migraine diagnosis were identified from either the direct care file or the purchased care file as described below.

The direct care file relied on Medical Expense Performance Reporting System (MEPRS) codes to identify where an episode of care was provided. The

coding was created to establish a uniform system for healthcare cost management within the Military Health System (MHS) (Department of Defense, 2001). Each three character MEPRS code corresponded to a defined a set of functional work centers which are summarized in Appendix B. The MEPRS code for emergency services (BIA) was the primary indicator of emergency care in the purchased care file (Department of Defense, 2001). Using this information, the Full Cost field was collected for each encounter (represented by FCR_SADR_BIA) to single out the costs of direct care provided in the emergency room.

The purchased care file had a similar field to distinguish where an episode of care occurred. The information was documented in the Place of Service field. Emergency room care was identified by the numeric code 23. The Amount Paid field was collected for each encounter (represented by APR_HCSR_23) to reflect the MHS cost of purchasing care in a non-MTF emergency department.

The formal definition for the total cost of emergency room care (TC_EMC) incurred during a 180 day study interval was calculated as follows:

$$TC\_EMC = \sum (FCR\_SADR\_BIA)_i + \sum (APR\_HCSR\_23)_i$$

where the subscripts represent the i^{th} claim for emergency room care during the pre-treatment, transitional, and post-treatment intervals respectively. In H_{05}, the analysis compared TC_EMC in the post-treatment interval only. For H_{11}, the change in the cost of emergency room care (ΔTC_EMC) was calculated as follows:

$$\Delta TC\_EMC = TC\_ERV_{post\text{-}treatment} - TC\_ERV_{transtional}$$

Total Cost of Ambulatory Services: This continuous variable represented the total cost of migraine-related outpatient medical care. For this study, outpatient medical care costs were limited to expenditures for non-emergent medical care, emergency room care, and prescription medication because they represent the major components of outpatient health care costs for migraineurs (Ferrari, 1998). Every subject was assigned a value for the total cost of migraine-related medical care incurred during each 180 day interval.

The formal definition for the total cost of migraine-related outpatient medical care (TC_AC) incurred during a 180 day study interval was calculated as follows:

$$TC\_AC = OP\_DC + TC\_NEMC + TC\_EMC$$

for the pre-treatment, transitional, and post-treatment intervals respectively. In H_{06}, the analysis compared TC_AC in the post-treatment interval only. For H_{12}, the change in the cost of ambulatory care (ΔTC_AC) was calculated as follows:

$$\Delta TC\_AC = TC\_AC_{post\text{-}treatment} - TC\_AC_{transtional}$$

Independent Variable

Daily Migraine Prevention: The focal independent variable was a dichotomous measure of whether or not an individual was exposed to daily

migraine prevention (1 = preventive cohort and 0 = comparison cohort). Exposure status was determined after identification of the migraine sample population. Subjects were partitioned into one of three mutually exclusive categories based on their use of daily migraine prevention (preventive medications defined in Table 2.3 on page 14). The process of cohort assignment is depicted graphically in Figure 4.3 below. The three categories included:

- Non Users: No exposure to daily migraine prevention during the 18 months of follow-up time (i.e., during the pre-treatment, transitional or post-treatment periods)
- New Users: First exposure to daily migraine prevention occurred after the index date during the transitional interval but not before (i.e., during the pre-treatment period)
- Other Users: First exposure to daily migraine prevention occurred before the index date (i.e., during the pre-treatment period) or during the post-treatment interval

The two groups of interest were the non users and new users. Other users were excluded because early exposure (i.e., during the pre-treatment interval) suggested that those subjects were at a different point in the progression of the disease and late exposure (I.e., during the post-treatment interval) did not provide enough follow-up time to generate measures of effect. As a result, the new users were classified as the study treatment group and the

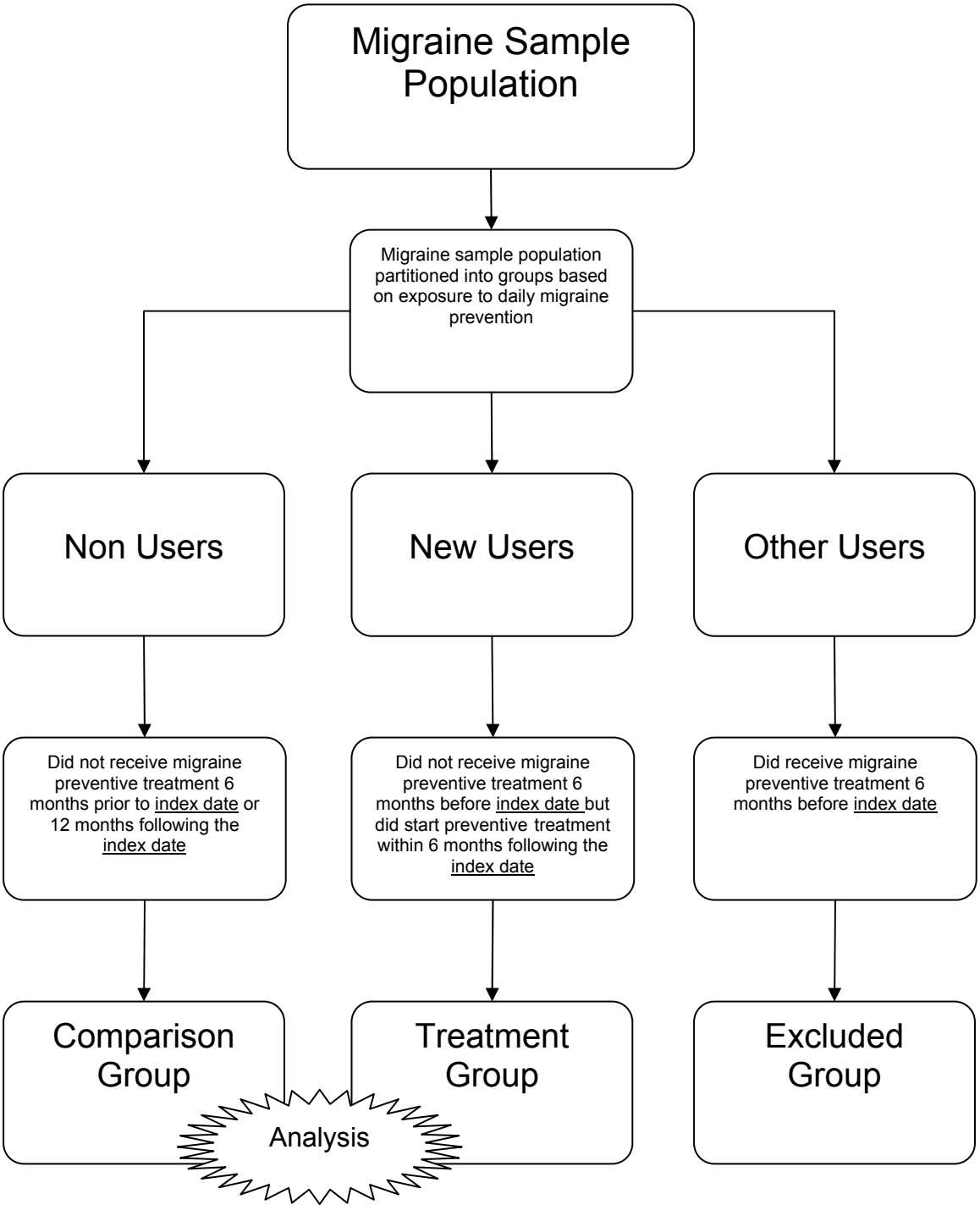
non users as the comparison group. Subjects in the treatment group were required to have had the first exposure to daily migraine prevention during the six month interval following the index date (i.e., during the transitional period) to insure at least 360 days follow-up time. The contrast of new users to non users was an interesting because it compared individuals who began treatment with daily migraine prevention to similar individuals who for unknown reasons did not receive treatment during the study period.

Control Variables

Selection of the study control variables was based on the Andersen Model of Health Care Utilization introduced in Chapter Three. As a brief review, the model predicts that health care utilization is a function of predisposing, enabling, and need characteristics (Andersen, 1995). Since its introduction in the late sixties the model has been adapted for a variety of health related applications. My use of the model was limited to identification of important confounders in the focal relationship.

Based on this premise, each control variable was included because of a theoretical potential to confound or modify the study focal relationship between daily migraine prevention and the primary outcome measures. Interaction and quadratic terms were included to allow for non-linear effects on the dependent variable and potential heterogeneity among study control variables. The remainder of this section describes each control variable used during analysis.

FIGURE 4.3. Flowchart of Cohort Assignment for Migraine Sample Population



Age: Age was included in the analysis as a predisposing characteristic. It was modeled as a continuous variable corresponding to each subject's age on the study-defined index date. Models that included age as an explanatory variable also evaluated the inclusion of a quadratic age term to allow for non-linear effects in the analysis.

Gender: Gender was classified as another predisposing characteristic. The dichotomous variable was dummy coded with men as the reference group (1 = women and 0 = men). An interaction of this variable with age also was considered during the data analysis.

Geographical Region: According to the model, geographical region was included as a predisposing characteristic. It was represented as a categorical variable signifying the TRICARE region a study subject was enrolled in at the time of the index date. At the time of the study, TRICARE had fifteen such regions around the globe. Ten regions fell within the continental United States (CONUS) and five regions were classified as outside the continental United States (OCONUS) (i.e., Alaska, Hawaii, Europe, or the Pacific). In order to maintain a reasonable number of geographic regions, the five regions classified outside the United States were grouped together in one category labeled OCONUS and the remaining ten CONUS regions were left unaltered. The

reference group consisted of individuals in the Northeast region. The regional categories as evaluated during this study are summarized in Table 4.3.

TABLE 4.3. TRICARE Health Service Region Names and the Areas Included in Each Region

Region Name	***States/Areas Included in Region***
Northeast	Northern Virginia, District of Columbia, Maryland, Delaware, Pennsylvania, New Jersey, New England States
Mid-Atlantic	Southern Virginia (south of Fredericksburg), North Carolina
Southeast	South Carolina, Georgia, Eastern Florida
Gulf South	Florida Panhandle, Eastern Louisiana, Alabama, Mississippi, Tennessee
Heartland	West Virginia, Ohio, Kentucky, Indiana, Illinois, Michigan, Wisconsin
Southwest	Western Louisiana, Arkansas, Oklahoma, Central and Eastern Texas
Central	Western Texas, Arizona, New Mexico, Nevada, Minnesota, Iowa, Missouri, Kansas, Nebraska, North and South Dakota, Montana, Wyoming, Colorado, Utah, and Idaho
So. California	Southern California
Golden Gate	Northern California
Northwest	Oregon, Washington
OCONUS	All areas outside the continental United States

Branch of Service: Branch of service was evaluated as a predisposing characteristic. It was modeled as a categorical variable corresponding to the Uniform Service of the United States that the sponsor was assigned while eligible for care in the MHS. The Uniform Services were categorized in the following manner: Army, Navy/Marine Corps, Air Force, and an other category which included the Coast Guard, Public Health Service, National Oceanic and Atmospheric Administration and individuals with an unknown branch of service.

The variable was derived from the branch of service reported in the data warehouse on the index date. The Army served as the reference group.

Beneficiary Category: Beneficiary category refers to a TRICARE designation that indicated how an individual patient was classified in the Military Health System (MHS). It was represented as a dichotomous variable and was used to differentiate between patients on Active Duty and all other eligible beneficiaries. The variable was represented by a dummy code with non-Active Duty status designated as the reference group. Individuals in the non-Active Duty category included Retirees, Dependents, Survivors, and Others. The variable was assigned according to an individual's status on the study defined index date.

Active duty status was identified as the most important contrast among beneficiary designations because subjects on active duty had priority over other beneficiary categories for care at Military Treatment Facilities (MTFs) and did not pay for any portion of their health care (i.e., no deductibles, premiums, or co-payments). Moreover, individuals on Active Duty were typically required to be healthier than other beneficiaries. For these reasons it seemed rational to think of beneficiary category as both an enabling and a predisposing characteristic.

Prescription Point of Service: Pharmacy services in the Military Health System were provided across three points of service during the study period. An

eligible beneficiary had the option to fill prescriptions at MTF pharmacies, in the retail network (e.g., local chain pharmacies), or through the TRICARE Mail Order Pharmacy (TMOP). The distinction was important because MTF pharmacies typically had a narrower formulary than the retail network or TMOP. Also, prescriptions filled in the retail network or through TMOP required a co-payment of $3 (generic) or $9 (brand) compared to MTFs which did not charge a co-payment for prescriptions. The variable was classified as an enabling characteristic.

A categorical variable was included in the model to estimate the influence of prescription point of service. The first group was the reference group and included individual's who had all prescriptions filled at MTF pharmacies during the study. The second group included individuals with fewer than 40% of their prescriptions filled outside of a MTF pharmacy during the study and the final group was made up of those patients that had greater than 40% of their prescriptions filled outside of a MTF pharmacy.

Type of Military Treatment Facility: The conceptual model suggested that characteristics of the medical facility that rendered care to an individual could influence both treatment decisions and utilization patterns. Hence, the primary enrollment site (i.e., Military Treatment Facility responsible for an individuals care) of each study subject was obtained from the administrative claims data

(i.e., HSCSR and SADR). The site was defined using information from the claim that was closest in absolute terms to the individual's index date.

With this information, a categorical variable was created to reflect the size of the individual's primary enrollment site. Facilities were grouped as either a clinic or a hospital based on TRICARE criteria summarized in Appendix C. In addition, the hospitals with medical residency programs were differentiated from non-teaching hospitals. This type of categorization allowed for a contrast between smaller facilities (i.e., clinics) to the largest medical facilities in the Military Health System (i.e., teaching hospitals). An additional category was included for individuals who did not receive health care from a MTF during the 18 month follow-up period. Type of facility was assumed to be fixed over the study period and the reference group consisted of clinics with dummy variables for non-teaching hospitals, hospitals with medical residency programs, and non-military facilities.

Comorbidity Measure: A variety of complex comorbidity indices have been developed and evaluated to control for underlying health status in research studies with observational designs. Comorbid illnesses were measured as a continuous variable derived by the number of unique prescription medication classes dispensed during the pre-treatment period. This method was recently shown to be a simple and efficient method for measuring comorbidity status and

predicting health care expenditures (Farley, Harley, & Devine, 2006; Perkins et al., 2004; Schneeweiss et al., 2001).

Measure of Migraine Disease Severity: Due to the aforementioned limitations of migraine prevention (i.e., prevention is generally reserved for patients with frequent or severe disease), not all individuals identified in the migraine population should be considered candidates for daily migraine prevention. Consequently, a measure of baseline disease severity was needed to control for pre-existing differences in the study cohorts. The best available estimate of migraine-specific disease severity in this data set was information on patients' utilization of migraine-specific abortive medication (MSAM) measured in Defined Daily Doses (DDD). The definition of a single DDD for each migraine-specific abortive medication was originally introduced in Table 4.2 above.

In addition to a standardized unit of measurement, the use of DDDs provided an approximation of each subject's headache frequency because a single DDD was designed to reflect the average amount of abortive medication required to treat a migraine headache in the average adult. As a result, the number of migraine headaches experienced during a defined time period could be inferred from patterns of MSAM use. The formal definition of this control variable included the amount of MSAM dispensed in DDDs during the pre-treatment interval. It was adopted as a baseline measure to control for pre-existing differences in disease severity and fit within the conceptual framework as

a need characteristic. A quadratic term was also evaluated in the model to allow for non-linear effects on the dependent variable.

Neurologist Care: Neurologist care was a dichotomous variable that indicated if an individual had at least one encounter with a neurologist during the pre-treatment period. The receipt of neurologist care was considered a need characteristic. The reference group consisted of patients who did not receive specialty care during the pre-treatment period.

TABLE 4.4. Summary of Study Variables

Study Variables	***Variable Type***
Dependent Variables	
Prescription Cost	continuous (in dollars)
MSAM Use	continuous (in defined daily doses)
Clinic Visit Costs	continuous (in dollars)
Emergency Room Visit Costs	continuous (in dollars)
Total Ambulatory Service Costs	continuous (in dollars)
Independent Variable	
Daily Migraine Prevention	dichotomous (1 = exposed, 0 = not exposed)
Control Variables	
Age	continuous (in years)
Age^2	continuous (in years)
Gender	dichotomous (1 = female, 0 = male)
Age * Gender	interaction term between age & gender
Geographic Region	categorical (corresponding TRICARE region)
Branch of Service	categorical (corresponding to uniformed service)
Beneficiary Category	dichotomous (1 = active duty, 0 = other)
Beneficiary Category * Gender	interaction term between beneficiary category & gender
Prescription Point of Service	categorical (MTF pharmacy vs. non-MTF pharmacy)
Type of Treatment Facility	categorical (clinic, hospital, or teaching hospital)
Comorbidity Measure	continuous (number of unique medications)
Comorbidity $Measure^2$	continuous (number of unique medications)
Migraine Severity	continuous (pre-treatment use of MSAM in DDD)
Migraine $Severity^2$	continuous (pre-treatment use of MSAM in DDD)
Neurologist Care	dichotomous (y/n, neurologist care during pre-index)

f. Statistical Considerations

Two years of claims data were used to estimate the effect of exposure to migraine prevention on health care expenditures during the transitional and post-treatment periods. The study hypotheses tested the assumption that individuals with migraine headaches exposed to prevention had similar rates of health care utilization than comparable individuals who received acute treatment alone. Analysis of the data was conducted in six steps as follows: (1) a descriptive investigation of the initial migraine sample population; (2) an examination of bivariate relationships between the focal independent variable with each control variable and primary outcome measure for included versus excluded subjects and new versus non users of migraine prevention; (3) a traditional multivariate model using ordinary least squares (OLS) linear regression to measure the effect of exposure to prevention on each outcome variable while controlling for observed confounders; (4) a matched sample analysis of treated and untreated subjects; (5) a sensitivity analysis for unobserved variable bias based on the results from the matched sample analysis; and (6) specification testing to examine the sensitivity of the results in the presence of common estimation difficulties associated with health care expenditures including non-normality, heteroskedasticity, presence of outliers, and censoring of the data at zero. The section on statistical considerations ends with a discussion and analysis of study power.

(1) Descriptive Investigation. The descriptive investigation included a summary of study variables. Continuous variables were described with a mean and standard deviation. Continuous variables with non-normal distributions were also described with median, inter-quartile range, and skewness statistics. All categorical variables were expressed as counts and percentages.

(2) Bivariate Analysis. The next step of the analysis compared the distribution of each dependent and control variable between the study treatment (new users of prevention) and comparison group (non users of prevention). Continuous variables were analyzed using independent t-tests and categorical variables were evaluated using chi-square tests. For each analysis, alpha was set at 0.05.

(3) Multivariate Analysis. Once the bivariate analysis was completed, hypothesis testing began with ordinary least squares (OLS) regression models for each outcome using the focal independent variable and all the control variable main effects as model predictors. The functional form for the cross-sectional model was based on the following specification:

$$Y_i = \beta_0 + \alpha T_i + \beta X_i + \mu$$

where Y_i was a measure of health care utilization during the post-index period, β_0 was an intercept term; T_i was a dichotomous variable that represented

exposure to migraine prevention (i.e., the focal independent variable), X_i was a vector of control variable main effects, β was a corresponding set of parameter estimates; and μ represented the model disturbance term. The regression parameter alpha (α) characterized the estimated effect of exposure to migraine prevention on the dependent variable adjusted for the vector of covariates. When traditional assumptions of OLS were met, this model was the best linear unbiased estimator of α (Kennedy, 2003). Throughout the results, the regression parameter of interest was α estimated for the treatment status dummy variable (T_i).

The longitudinal model functional form was slightly different than the cross-sectional model. The results for the longitudinal hypotheses were generated from the following model specification:

$$\Delta Y_i = \beta_0 + \alpha T_i + \beta X_i + \mu$$

where ΔY_i was the change in expenditures from the transitional interval to the post-treatment interval calculated for each subject by subtracting their transitional expenditures from their post-treatment expenditures. The explanatory variables on the right hand side of the model were similar to the cross-sectional model right hand side variables.

(4) Matched Analysis. Use of matching offered several theoretical and practical advantages over traditional regression adjustment (Glynn, Schneeweiss, & Sturmer, 2006). As a result, we used propensity scores as a multivariate matching technique to create 1 to 1 matched sample of new and non users of daily migraine prevention. The remainder of this section assumes that the aforementioned "strong ignorability" assumption held for the data at hand. In the next section (f), the assumption of strong ignorability was relaxed to examine how the strength of the estimated treatment effects might change.

The strong ignorability assumption was implied by the computation of the propensity score for each individual in the study population. Based on this assumption, the propensity score was interpreted as the conditional probability of exposure to treatment given the vector of observed covariates (Rosenbaum & Rubin, 1983). Estimation of the score was accomplished via a logistic regression to determine the probability of exposure during the transition period. The outcome was identified as (0=not exposed to prevention, 1=exposed to prevention). The functional form for the logistic regression model was as follows:

$$q(X) = \Pr(T = 1) \mid X = \exp(\beta_0 + \beta X) / [1 + \exp(\beta_0 + \beta X)]$$

where $q(X)$ was the estimated probability of exposure to treatment (T) with daily migraine prevention, β_0 was the intercept, X was a vector of control variables, and β was corresponding vector of parameter estimates. The propensity score

was equal to $q(X)$. Rosenbaum and Rubin (1983) showed that matching treated subjects with controls using the propensity score will, on expectation, remove the bias due to the observed covariates. However, it should be noted that this process did not make any guarantees about the distribution of unobserved characteristics in the treatment and comparison group.

Two separate propensity scores were estimated prior to hypothesis testing to create two distinct matched samples for the analysis. The first sample was used to measure treatment effects for the cross-sectional hypotheses (i.e., those hypotheses comparing post-treatment outcomes only). This specification included predictors from the preceding interval such as migraine-specific abortive medication use and headache related costs from the transitional interval. A second propensity score specification was necessary because several of the explanatory variables used in the first specification were included in the dependent variable in the longitudinal hypotheses (i.e., transitional MSAM use). The longitudinal hypotheses were evaluated by comparing differences in outcomes. Each difference was obtained by subtracting transitional use from post-treatment use. Hence, transitional variables from the first specification were substituted with pre-treatment variables and another propensity score was generated for analysis of the longitudinal hypotheses.

Once the propensity scores had been estimated, balanced samples were created using a caliper matching algorithm (Becker & Ichino, 2002). After randomly ordering observations, control subjects with a propensity score that fell

within the pre-defined radius of each treated subject's propensity score were selected. The control subject with the propensity score that was closest in absolute terms to the score of the treated unit was then selected without replacement. This matching process resulted in more homogenous subject pairs than other more commonly used strategies such as nearest neighbor matching. The propensity score radius was defined as follows (Rosenbaum & Rubin, 1985):

$$\left| q(X)_{treated} - q(X)_{control} \right| \leq 0.60 * S_{q(X)}$$

where $q(X)$ was the predicted probability of exposure to daily migraine prevention and $S_{q(X)}$ was the pooled standard deviation of the $q(X)$.

A treated unit was designated as unmatched and removed from the sample if the process failed to identify at least one control subject within the radius defined above. After running each treated subject through the matching process, the effectiveness of the procedure was assessed by comparing two-sample t-statistics and the standardized percentage difference (D'Agostino, 1998) among study covariates for matched treated and control subjects. The standardized percentage difference between treatment and controls was calculated as follows:

$$D_i = 100\left(X_t - X_c\right) / \sqrt{[(S_t^2 + S_c^2)/2]}$$

where X_t and X_c are the covariate means and S_t^2 and S_c^2 are the sample variances of the i[th] covariate for the treatment and control groups respectively.

The estimated effects after caliper matching were the primary findings from which this study made inferences. However, because caliper matching excluded some treated subjects, estimated measures of effect for hypothesis testing were also derived using nearest-neighbor matching. This approach was less restrictive than caliper matching because it did not require the matches to occur within a pre-defined range. Instead, it took the closest control subject to each treated subject on the region of common support regardless of the absolute difference in estimated propensity scores. This method created more matches (i.e., it enhances the precision of the estimated effect) but also increased the bias due to observable characteristics. Still, it was a useful specification test to consider the relative importance of the matching algorithm when interpreting the study results.

The measures of effect generated from propensity score matched samples were examples of the average treatment effect among the treated subjects (ATT). Following Becker and Ichino (2002), the ATT after caliper and nearest neighbor matching was generated from the following estimator:

$$ATT^M = \frac{1}{N^T}\sum_{i \in T} Y_i^T - \frac{1}{N^T}\sum_{i \in T} w_j Y_j^C$$

where ATT^M was the average treatment effect among the treated generated from matching algorithm ^{M} (i.e., caliper or nearest neighbor). N^T was the number of matched treated subjects, Y_i^T was the outcome of interest for the ith subject in the new user cohort, w_j was the weight assigned to each comparison subject (e.g., equal to one if the subject was successfully matched and zero otherwise), and Y_j^C was the outcome of interest for the ith subject in the non user cohort.

Propensity score derivation and estimation of the ATT for each outcome was accomplished with the PSMATCH2 module for STATA 9.0 (Leuven & Sianesi, 2003). Standard errors and 95% confidence regions for matched sample estimates were computed using a bootstrap with 250 replications. All parameter estimates for the ATT were reported in conjunction with the OLS estimates to evaluate the strength and sensitivity of the results to bias from observed characteristics.

(5) Sensitivity Analysis for Unobserved Variable Bias. Estimation of treatment effects in sections d and e were followed by a sensitivity analysis to examine the strength of the results to unobserved or hidden variable bias using a method outlined by Rosenbaum (2002). The analysis was limited to measures of effect (α) estimated from the matched analysis (section e) because a priori, these

estimates were expected to provide a better description of the study treatment effects.

Rosenbaum (2002) recommended conducting a sensitivity analysis using a measure called Γ which can be interpreted as how much deviation existed from the assumption of no hidden bias (i.e., equal treatment probabilities between matched pairs). More formally, the measure Γ was defined as the odds ratio of receiving treatment for individual participants matched in the previous section. If the assumption of no hidden bias held, then Γ = 1 and the estimated treatment effect was an unbiased estimate of the true treatment effect. However, if hidden bias was present in the analysis, then Γ was not equal to 1 which suggested that two matched individuals who appeared similar on **X** actually had different treatment probabilities. For example, Γ = 2 would indicate that within each matched pair, the odds of receiving the treatment of interest varied by a factor of two (i.e., the odds of receiving treatment among the treated is two times the odds of receiving treatment among the controls).

Using this information, Γ was varied over a range of plausible values to determine how inferences might change in the presence of an unobserved covariate. For continuous outcomes in a matched analysis, Rosenbaum (2002) recommended the sensitivity analysis be based on Wilcoxon's signed rank test. With this approach, an estimate of the lower and upper bound of significance levels derived from the signed rank test can be determined for each value of gamma. In other words, one can estimate a range of plausible significance

levels for a given quantity of Γ. The results of the sensitivity analysis reported the value of Γ where estimated treatment effects were no longer statistically significant (i.e., $p > 0.05$). This information was used to discuss how inferences from study results might have changed in the presence of unobserved variable bias.

(6) Model Specification Testing. Modeling health expenditure data in this observational study led to violations of the traditional OLS regression assumptions. Although discussed at the end of the data analysis plan, model specification testing was used frequently throughout sections d and e to identify the appropriate functional form. The most common violations observed during the dissertation are discussed below along with the corrections used to evaluate the sensitivity of the OLS regression parameters. Whenever possible, the study followed recommendations from previous work compared treatment costs for anti-depressant therapy from retrospective administrative claims data (Berndt et al., 2000).

Normality of the error term was tested visually with a histogram of the model residuals and logarithmic transformations of the dependent variable were applied as necessary. Heteroskedasticity of the residuals was examined by visual inspection of the estimated residual against predicted values and with a Cook-Weisberg test (Greene, 2002; Kennedy, 2003). In addition to the logarithmic transformation of the dependent variable, models also were estimated using of heteroskedasticity-consistent standard errors.

Influential observations were identified using the Belsley, Kuh, and Welsch (1980) procedure (BKW). This procedure identified observations that meet two criteria: (1) the influential observation must have had a studentized residual greater than 2 in absolute terms; and (2) the influential observation must have had a leverage value more than two times the average where the average leverage was defined as the number of predictors divided by the number of observations. The importance of outliers were evaluated through a comparison of the least squares estimates to a trimmed sample (i.e., outliers identified by BKW procedure dropped) regression model. The change in parameter estimates were reported to examine the weight of influential data points.

Finally, lack of random assignment violated of the assumption that the expected value of the residuals was equal to zero. Without this assumption, it can be shown parameter estimates generated by OLS are biased. This required an estimation technique that could adjust for the potential bias. Two strategies were proposed to address this problem. First, propensity scores were used to conduct a matched sample analysis with a number of observed variables thought to be important when evaluating health care utilization. Correlation of unobserved variables with observed factors included in the matched sample analysis provided a better estimate of the treatment effect in the absence of random assignment. However, because this was an untestable assumption, the results were also subjected to the previously discussed sensitivity analysis to

assess the potential influence of unobserved variables on the qualitative and quantitative study conclusions.

Power Considerations. The study power analysis was conducted with GPOWER across multiple betas and varying alphas (Erdfelder, Faul, & Buchner, 1996). The results are summarized in Table 4.5. Analysis of power indicated that in order to observe a moderate effect with multiple regression and 25 predictors, the study would need a sample size between 172 – 302 subjects. Because the smallest sample size from which treatment effects were estimated was 1,658 subjects (i.e., the matched sample), the dissertation should have sufficient power for detection a moderate effect with both traditional regression models and the matched sample analysis.

TABLE 4.5. Power Analysis for Study Hypotheses

	Potential Alpha Levels (2-tailed)		
***Power* (1 – β)**	***0.05***	***0.02***	***0.01***
0.80	172	204	227
0.90	209	243	267
0.95	241	277	302

h. Human Subjects Research

Protection of Human Subjects. The proposed study received IRB approval from the University of Minnesota and Brooks City Air Force Base. The study

data was governed by a Data Use Agreement that specified how the information was handled. The analytic data set was de-identified and stored in encrypted format on an external hard drive. Furthermore, the data was only accessible to the primary investigator and was locked in a secure cabinet when not in use.

Inclusion of Women. The study topic is of particular interest to women because women experience migraines at a rate three times that of men. Women were included in the analysis if they meet other study inclusion criteria. No specific techniques were employed to sample equal numbers of men and women. Instead, the sample was driven by individuals who currently receive care for migraine.

Inclusion of Minorities. The study did not contain specific provisions to either include or exclude minorities. Furthermore, the race data contained in the database was largely missing with the available data reported to be largely inaccurate. This limited the ability to assess the impact of migraine between individuals of different races or ethnicity.

Inclusion of Children. Based on the NIH definition of children, individuals between the ages of 17 – 21 were included in the study. Children less than seventeen years of age were excluded because clinical information supporting the safety and efficacy of daily migraine prevention in this population was

unavailable. Despite this exclusion, the concept remains an important topic and an area that warrants additional study.

Chapter 5

RESULTS

a. Overview of Results

The study results are organized into the following sections: (1) characteristics of the initial migraine sample population; (2) identification of the study cohorts; (3) descriptive analysis of study variables stratified by cohort assignment for included subjects only; (4) derivation of the propensity score and matched sample; (5) estimated effect of exposure to migraine prevention on utilization during the post-treatment period (cross-sectional hypotheses); (6) estimated effect of exposure to migraine prevention on the change in utilization from the transitional to the post-treatment period (longitudinal hypotheses); (7) sensitivity analysis of the estimated treatment effects to unobserved variable bias.

b. Characteristics of the Initial Migraine Sample Population

The migraine sample population contained 8,436 patients. The population characteristics are summarized in Table 5.1. The subjects were predominately female (82%) classified as other than active duty (75%) with an average age of 37 years (Table 5.1). The assigned branch of service was equally distributed

TABLE 5.1. Characteristics of the Initial Migraine Sample Population

	Migraine Sample	
	(n = 8,436)	
Characteristic	**Count**	**%**
Age (in years)[a]	37.5	11.71
Female	6,946	82.34
Beneficiary Category		
Active Duty	2,093	24.81
Other	6,343	75.19
Branch of Service		
Army	2,738	32.46
Air Force	2,630	31.18
Navy/Marine	2,876	34.09
Other	192	2.28
Geographic Region		
Northeast	753	8.93
Mid-Atlantic	1,523	18.05
Southeast	1,080	12.81
Gulf South	758	8.99
Heartland	514	6.09
Southwest	853	10.11
Central	1,264	14.98
Southern California	457	5.42
Golden Gate	195	2.31
Northwest	335	3.97
Overseas	704	8.35
Treatment Facility		
Clinic	2,661	31.54
Hospital	1,538	18.23
Teaching Hospital	2,250	26.67
Non-Military Facility	1,987	23.55
Prescription Service		
MTF Only	2,796	33.14
Low Retail	2,766	32.79
High Retail	2,874	34.07
MSAM Use (in DDD)[a,b]	25.1	54.35
Comorbidity Index (in unique prescriptions)[a,b]	10.7	6.97
Neurologist Care[b]	2,260	26.79

Note. MSAM = migraine-specific abortive medication; DDD = defined daily dose. [a] mean (SD).

[b] characteristic determined from pre-treatment interval only.

across the Army, Air Force, and Navy/Marine Corps with less than 3% of study subjects coming from one of the other Uniformed Services (Table 5.1). The majority of the migraine population was stationed within the continental United States (92%) with the remainder assigned outside the continental United States. From within the United States, subjects were more likely to be assigned in the Mid-Atlantic (18%), Central (15%), Southeast (13%), and Southwest (10%) TRICARE regions (Table 5.1). All other regions accounted for fewer than 10 percent of the migraine sample population.

More than three-fourths of study subjects received health care services from a Military Treatment Facility (MTF) (Table 5.1). This included facilities designated as either a clinic or hospital with 32% and 45% of study population respectively. Patients were more likely to receive care from a hospital with post-graduate medical education (27%) than a non-teaching hospital (18%). Twenty-three percent had all health care services rendered outside of the direct care environment in the Military Health System.

The majority of study subjects used multiple points of service to access prescription medications during the study. One-third of the population received medication form MTF pharmacies only (Table 5.1). The remaining two-thirds had at least one prescription filled outside the MTF pharmacy defined as either a pharmacy from the retail network or from the TRICARE Mail Order Pharmacy (Table 5.1). For all retail users, approximately one-half were classified as low retail users. This corresponded to an individual who received fewer than 40% of

filled prescriptions from the retail point of service. The remaining subjects were classified as high retail users with more than 40% of filled prescriptions from the retail point of service.

The patient population used a variety of prescription medications during the pre-treatment period (i.e., the 6 month period immediately preceding the study-defined index date). The average patient received approximately 11 unique prescription and over-the-counter medications during the 6 month interval (Table 5.1). Similarly, the average patient received 25 Defined Daily Doses (DDD) of migraine-specific abortive medications during the pre-treatment period with a mean rate of utilization at 4 DDDs per month (Table 5.1). Use of neurologist care prior to the index date also was evaluated. Twenty-seven percent of study subjects in the initial migraine sample had at least one encounter with a neurologist during the pre-treatment period (Table 5.1).

The average amount of ambulatory health care consumed by the initial sample population during the pre-treatment interal is summarized in Table 5.2. All expenditures are reported per member and occurred over a 180 day period. The results showed that non-emergent outpatient care was the most costly category, followed by spending on prescription drugs and emergency services, respectively. Limiting utilization to migraine-related claims changed the order somewhat. It identified prescription expenditures as the most costly category responsible for as much as 54% of migraine-related ambulatory care. This was followed by non-emergent outpatient care and finally, emergency room care.

TABLE 5.2. Pre-Treatment Ambulatory Health Care Spending Patterns of the Initial Migraine Sample Population

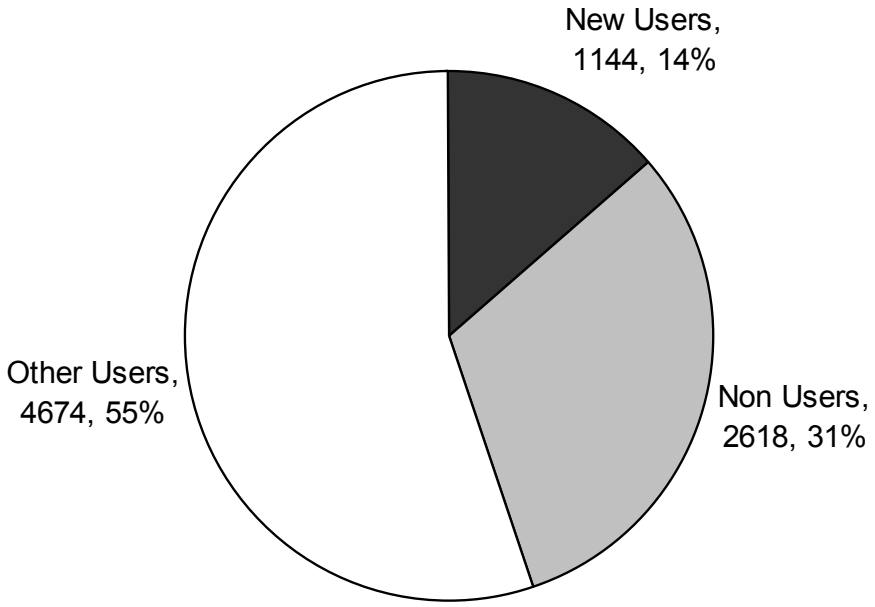
	Migraine Sample (n = 8,436)	
Category	**Mean[a]**	**SD**
Prescription		
Definitely Migraine Related	243.55	594.97
Potentially Migraine Related	300.48	620.70
Total Prescription	946.01	1,990.49
Non-Emergent Outpatient Care		
Migraine Only	373.04	760.20
All Cause	2,030.81	2,920.31
Emergency Room Care		
Migraine Only	89.75	457.58
All Cause	198.18	696.44
Total Ambulatory Care		
Migraine Only	1,006.81	1,469.14
All Cause	3,174.99	3,956.01

Note. [a] expenditures measured in unadjusted US $ expressed per member per 180 day interval

c. Identification of the Study Cohorts

Each individual identified from the migraine sample population was classified into one of three mutually exclusive categories determined by the person's prescription profile. The categories indicated if and when an individual used daily migraine prevention during the study period. Categories were labeled as new users, non users, and other users. The number and proportion of subjects in each category is summarized in Figure 5.1.

FIGURE 5.1. Cohort Membership of the Initial Migraine Sample Population



The study compared measures of resource utilization between new and non users (3,762 subjects) of daily migraine prevention. The category of other users consisted of subjects who received daily migraine prevention prior to the study defined index date or during the post-treatment period. The other users were excluded because of concerns that they were at a different point in disease progression compared to new users. The results of a descriptive comparison between included and excluded study subjects are summarized in Appendix D.

d. Descriptive Analysis of Study Variables Stratified by Cohort Assignment

Tables 5.3 and 5.4 compare the pre-treatment characteristics for new and non users of daily migraine prevention. Patient groups were similar with respect to the sponsor's assigned branch of service and use of migraine-specific abortive medication measured in Defined Daily Doses. However, all other characteristics showed varying degrees of imbalance between groups.

TABLE 5.3. Comparison of Continuous Characteristics for New Users and Non Users of Daily Migraine Prevention (N = 3,762)

	New Users		***Non Users***			
	(n = 1,144)		**(n = 2,618)**		***Comparisons***	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	d_i	***t***
Age (years)	34.5	11.33	36.4	11.95	-16.50	4.6**
Pre-Treatment MSAM Use[a]	16.4	45.76	15.8	37.8	1.45	-0.4
Pre-Treatment Comorbidity[b]	11.1	6.69	7.7	5.40	55.92	-16.5**

Note. d_i = Standardized percent difference. [a] migraine-specific abortive medication (MSAM) measured in Defined Daily Doses (DDD). [b] a count of unique prescription medications received

* $p < 0.05$. ** $p < 0.01$.

TABLE 5.4. Comparison of Categorical Characteristics for New Users and Non Users of Daily Migraine Prevention (N = 3,762)

	New Users		***Non Users***			
	(n = 1,144)		***(n = 2,618)***		***Comparisons***	
Characteristic	**Count**	**%**	**Count**	**%**	d_i	χ^2
Female	893	78.06	2164	82.66	-11.59	11.1**
Beneficiary Category						
Active Duty	371	32.43	669	25.55	15.19	
Other	773	67.57	1949	74.45	-15.19	18.8**
Branch of Service						
Army	391	34.18	873	33.35	1.76	
Air Force	331	28.93	782	29.87	-2.06	
Navy/Marine	400	34.97	905	34.57	0.83	
Other	22	1.92	58	2.22	-2.05	0.8
Geographic Region						
Northeast	99	8.65	259	9.89	-4.27	
Mid-Atlantic	214	18.71	438	16.73	5.18	
Southeast	136	11.89	321	12.26	-1.14	
Gulf South	78	6.82	242	9.24	-8.93	
Heartland	87	7.61	130	4.97	10.89	
Southwest	102	8.92	256	9.78	-2.96	
Central	168	14.69	401	15.32	-1.77	
Southern California	65	5.68	163	6.23	-2.30	
Golden Gate	33	2.88	54	2.06	5.29	
Northwest	51	4.46	93	3.55	4.62	
Overseas	111	9.70	261	9.97	-0.90	23.6**
Treatment Facility						
Clinic	348	30.42	973	37.17	-14.29	
Hospital	241	21.07	426	16.27	12.32	
Teaching Hospital	351	30.68	524	20.02	24.70	
Non-Military Facility	204	17.83	695	26.55	-21.08	84.9**
Prescription Service						
MTF Only	409	35.75	1044	39.88	-8.51	
Low Retail	415	36.28	676	25.82	22.73	
High Retail	320	27.97	898	34.30	-13.70	43.4**
Pre-Treatment Specialist	330	28.85	330	12.61	40.88	145.2**

Note. d_i = Standardized percent difference. * $p < 0.05$. ** $p < 0.01$.

Subjects in the non user cohort had a slightly higher percentage of females and were older by two years on average (Table 5.4). The geographic distribution was similar in most areas with the largest differences occurring in the Heartland and Gulf South regions (Table 5.4). Based on standardized percentages, pre-treatment specialty care and degree of comorbidity showed the most evidence of imbalance. New users were more likely to receive pre-treatment specialty care and showed greater evidence of pre-treatment comorbidity (Table 5.3 & Table 5.4).

Table 5.5 describes mean health care spending over a 180 day interval for both new and non users of daily migraine prevention. Each category includes both migraine-related and total health care expenditures. Without exception, the new user cohort experienced higher rates of spending in each category. Non-emergent outpatient care costs accounted for the largest difference followed by the cost of prescription drugs. The pattern was consistent for migraine-specific costs as well as total health care costs.

Figure 5.2 depicts migraine-related expenditures as a percent of the total health care spending during the study period stratified by cohort. On average, migraine-related costs accounted for a larger percentage of total spending among new users of daily migraine prevention. In comparison, the cohort of non users had less than one-quarter of total health care costs consumed in the treatment of migraine.

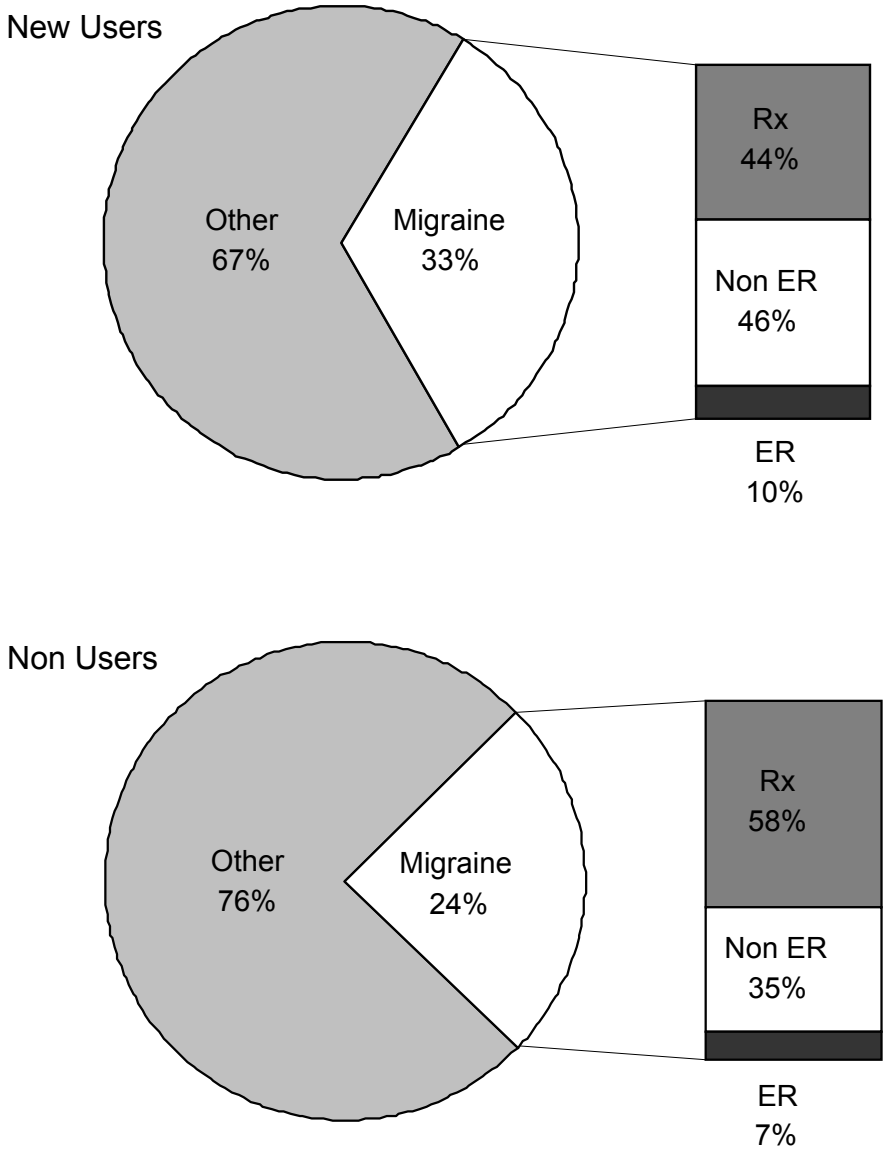
TABLE 5.5. Summary of Mean Ambulatory Health Care Spending for New Users and Non Users of Daily Migraine Prevention (N = 3,762)

	New Users		***Non Users***	
	(n = 1,144)		***(n = 2,618)***	
Characteristic	**Mean[a]**	**SD**	**Mean[a]**	**SD**
Prescription				
Definitely Migraine Related	267.83	588.60	175.17	398.11
Potentially Migraine Related	274.56	605.33	140.41	396.03
Total Prescription	962.73	2,922.01	607.29	1,025.88
Non-Emergent Outpatient Care				
Migraine Only	569.51	1,084.10	187.62	431.48
All Cause	2,488.70	3,231.35	1,482.49	2,210.51
Emergency Room Care				
Migraine Only	117.47	480.08	40.72	190.80
All Cause	266.46	755.90	116.63	334.14
Total Ambulatory Care				
Migraine Only	1,229.37	1,788.04	543.52	829.89
All Cause	3,718.95	4,884.23	2,206.94	2,652.06

[a] expenditures measured in unadjusted US $ expressed as per member per 180 days

* $p < 0.05$. ** $p < 0.01$.

FIGURE 5.2. Migraine-Related Expenditures as a Percentage of Total Spending for New and Non Users of Daily Migraine Prevention (N = 3,762)



Note. Other = non migraine expenditures; Rx = prescription expenditures; non ER = non-emergent health care expenditures; ER = emergency room expenditures

Figure 5.2 also shows the percent allocation of migraine-related spending across the three major outpatient cost categories. Among new users of daily migraine prevention, the majority of migraine-related costs accrued from non-drug services responsible (i.e., emergent and non-emergent outpatient care) for 56% of spending. Cost of prescription drugs accounted for the remaining 44% of spending in this group. The pattern in the non user cohort differed somewhat with the majority of migraine-related costs attributable to prescription drugs (58%). Spending on non-drug services was responsible for a smaller percentage of all migraine-related costs (42%) in the non user cohort.

A more detailed examination of migraine-related utilization by study interval (i.e., pre-treatment, transitional, and post-treatment) is summarized in Table 5.6. With the exception of migraine-specific abortive medication use, the new user cohort spent more on migraine-related care than did the non users during the pre-treatment interval. This trend continued in each study interval.

Average utilization in each category peaked during the transitional period for both cohorts and declined somewhat in the post-treatment interval. However, in most categories spending did not return to the levels observed during the pre-treatment period. The table also shows the average change in utilization from the transitional period to the post-treatment period.

TABLE 5.6. Mean Migraine-Related Utilization by Study Interval for New and Non Users of Daily Migraine Prevention (N = 3,762)

	New Users (n = 1,144)			***Non Users*** (n = 2,618)		
Characteristic	**Mean**	**SD**	**Maximum**	**Mean**	**SD**	**Maximum**
Rx – Definitely Related						
Pre-Treatment	168.73	507.26	7,908.50	151.17	386.51	6,311.99
Transitional (T)	364.62	623.07	7,550.41	197.69	419.40	7,933.81
Post-Treatment (P)	270.13	635.47	11,659.29	175.44	387.42	8,103.75
Difference (P–T)	-94.49	458.38	4,330.22	-22.26	258.75	1,551.48
Rx – Potentially Related						
Pre-Treatment	145.54	418.97	6,158.84	114.68	318.19	6,343.90
Transitional (T)	323.16	601.10	8,785.30	146.07	403.40	7,812.27
Post-Treatment (P)	354.98	795.93	17,462.59	160.49	466.51	12,629.26
Difference (P–T)	31.81	576.49	11,328.06	14.42	218.93	4,816.99
MSAM Utilization						
Pre-Treatment	16.4	55.75	648.00	23.87	42.80	621.00
Transitional (T)	39.84	57.12	819.00	22.64	43.14	648.00
Post-Treatment (P)	30.63	51.48	540.00	21.41	41.40	738.00
Difference (P–T)	-9.87	56.92	540.00	-1.62	34.36	285.00
Non-Emergent Care						
Pre-Treatment	296.99	808.28	15,363.83	189.23	424.38	6,193.53
Transitional (T)	899.86	1,273.31	14,758.91	219.84	432.77	5,444.31
Post-Treatment (P)	511.68	1,170.73	14,709.01	153.80	437.28	7,646.35
Difference (P–T)	-388.18	1,275.39	9,725.58	-66.04	545.15	7,646.35
Emergency Room Care						
Pre-Treatment	89.72	365.73	6,681.75	43.81	169.69	2,611.81
Transitional (T)	159.87	558.35	8,713.81	40.95	192.29	4,212.22
Post-Treatment (P)	102.82	516.17	9,350.34	37.40	210.43	6,088.07
Difference (P–T)	-57.05	532.95	4,602.79	-3.56	223.13	5,203.36
Total Ambulatory Care						
Pre-Treatment	700.98	1,379.57	22,688.08	498.90	755.37	9,789.84
Transitional (T)	1,747.51	1,928.48	27,847.47	604.55	845.36	10,375.68
Post-Treatment (P)	1,239.61	2,056.09	31,169.98	527.12	888.94	13,062.39
Difference (P–T)	-507.91	1,806.52	15,252.77	-77.44	758.69	11,681.13

Note. Rx = prescription; MSAM = Migraine-specific abortive medication. [a] measured in Defined Daily Doses (DDD).

TABLE 5.7. Median, Inter-Quartile Range, and Censoring at Zero of Migraine-Related Health Care Utilization by Study Interval for New and Non Users of Daily Migraine Prevention (N = 3,762)

	New Users (n = 1,144)			***Non Users*** (n = 2,618)		
Characteristic	**Median**	**IQR**	**% Zero**	**Median**	**IQR**	**% Zero**
Rx – Definitely Related						
Pre-Treatment	0	0 – 106.92	58.5	0	0 – 132.70	52.9
Transitional	166.37	38.10 – 447.12	15.4	41.70	0 – 241.58	36.6
Post-Treatment	42.18	0 – 317.18	39.2	4.46	0 – 187.44	46.3
Difference (P–T)	-40.31	-211.46 – 13.88	n/a	0	-78.19 – 18.93	n/a
Rx – Potentially Related						
Pre-Treatment	7.03	0.45 – 128.17	21.9	4.25	0 – 96.05	30.3
Transitional	135.48	32.27 – 363.70	0	7.80	0 – 140.30	27.6
Post-Treatment	106.94	5.04 – 406.82	14.2	5.85	0 – 136.11	32.1
Difference (P–T)	-3.85	-93.60 – 96.58	n/a	0	-12.18 – 20.39	n/a
MSAM Utilization						
Pre-Treatment	n/a	0 – 12	58.5	n/a	0 – 18	52.9
Transitional	24	8 – 52	15.4	9	0 – 27	36.6
Post-Treatment	10	0 – 36	39.2	6	0 – 26	46.3
Difference (P–T)	-6	-24 – 4.5	n/a	n/a	-9 – 6	n/a
Non-Emergent Care						
Pre-Treatment	29.38	0 – 319.01	47.9	n/a	0 – 238.84	55.5
Transitional	556.49	166.76 – 1,145.63	12.4	n/a	0 – 275.01	52.4
Post-Treatment	109.95	0 – 569.76	39.7	n/a	0 – 141.94	63.9
Difference (P–T)	-231.45	-789.12 – 15.04		n/a	-177.72 – 0	n/a
Emergency Care						
Pre-Treatment	n/a	n/a	82.6	n/a	n/a	87.7
Transitional	n/a	n/a	77.0	n/a	n/a	89.6
Post-Treatment	n/a	n/a	85.2	n/a	n/a	91.2
Difference (P–T)	n/a	n/a	n/a	n/a	n/a	n/a
Total Ambulatory Care						
Pre-Treatment	306.89	15.88 – 820.39	11.4	252.47	7.24 – 654.01	14.6
Transitional	1,233.27	621.43 – 2,231.58	0	345.00	60.93 – 804.68	10.5
Post-Treatment	664.58	175.00 – 1,507.12	9.3	260.74	4.49 – 652.91	17.8
Difference (P–T)	-398.97	-1,201.23 – 130.25	n/a	-6.21	-307.73–160.0	n/a

Note. Rx = prescription; MSAM = Migraine-specific abortive medication; IQR = Inter-Quartile Range; % Zero = percent of subjects at zero in cohort. [a] measured in Defined Daily Doses (DDD).

Table 5.7 describes the median, inter-quartile range and percentage of cases censored at zero for migraine-related health care utilization during each study interval. Median pre-treatment period expenditures were similar in each group. However, expenditures diverged during transitional and post-treatment periods. In each case, new users of daily migraine prevention required significantly more resources than did the cohort of non users. The largest difference was observed in payments for non-emergent care followed by spending on prescription medication.

The degree of censoring at zero varied widely by category of care and study interval. Emergency room costs displayed the greatest amount of left censoring with more than three-fourths of all subjects reporting no emergent care expenditures during the study intervals. The distribution of each outcome also showed evidence of significant right tail skewness as evidenced by median values smaller than means and measures of skewness being positive and large (data not shown) suggesting that results from statistical tests based on an assumption of normality be interpreted cautiously.

e. Derivation of the Propensity Score and Matched Sample

Prior to hypothesis testing, propensity scores were estimated to create two matched samples (i.e., one for the cross-sectional hypotheses and one for the longitudinal hypotheses). Both were generated in a similar fashion. The primary difference was the specification of the propensity score. Treatment probabilities

for the two matched samples were estimated with a slightly different set of covariates (i.e., pre-treatment vs. transitional utilization measures). This was done to avoid over-matching because the longitudinal outcomes included measures of utilization from the transitional interval. Hence, the matched sample used to evaluate the longitudinal hypotheses used pre-treatment measures in place of transitional utilization measures to estimate the probability of treatment. Derivation of the propensity score and the matching algorithm used to identify the matched sample for the cross sectional hypotheses are discussed in detail throughout this section. The results for the longitudinal hypotheses are summarized in Appendix E. The implications of two separate matched samples are discussed at the end of this section.

Table 5.8 summarizes the results from the logit model used in the cross-sectional hypotheses. Once the model was specified, each subjects predicted probability of treatment was determined based on their unique set of observed characteristics. These predicted probabilities were defined as the propensity scores for the cross-sectional hypotheses.

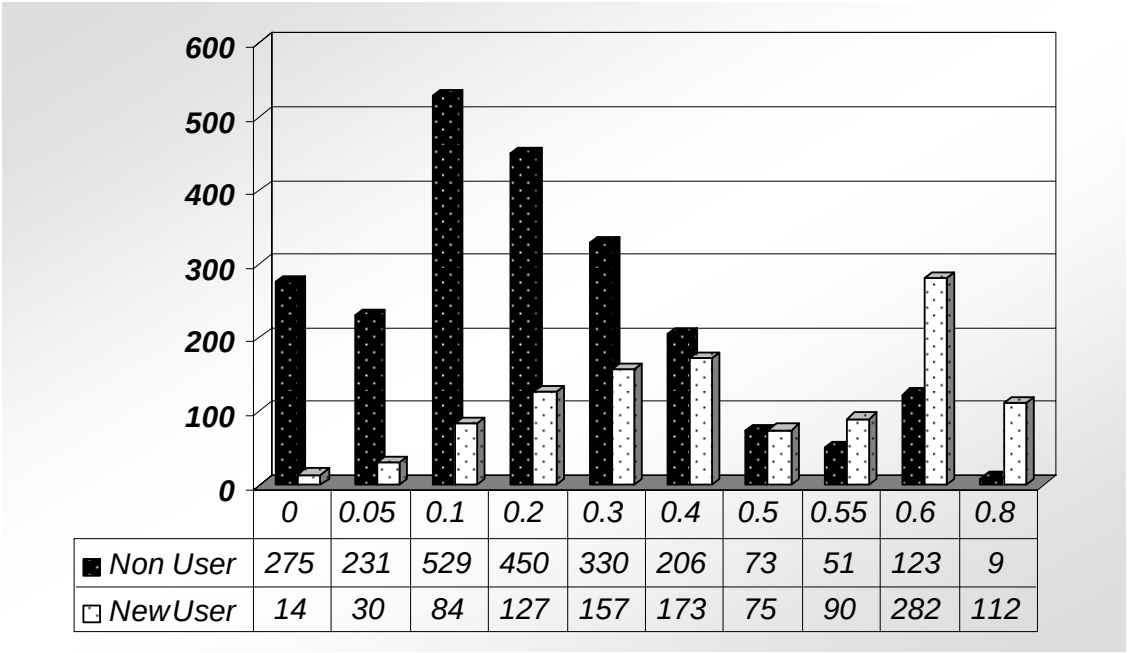
Figure 5.3 shows a histogram of estimated propensity scores for both new and non users of daily migraine prevention stratified by inferior block of the propensity score. As expected, the distribution of predicted probabilities was higher for new users than for non users. In addition, as the propensity score increased, the number of non users available for a close proximity match (i.e., within a defined caliper) declined.

TABLE 5.8. Logistic Regression Model Estimating the Conditional Probability of Exposure to Daily Migraine Prevention for Cross-Sectional Hypotheses

Matching Variables	***Coefficient****	***Standard Error***
Age	-0.011	0.024
Age Squared	$9.9e^{-5}$	$2.9e^{-4}$
Female	0.941[a]	0.480
Age * Gender (interaction)	-0.024[a]	0.010
TRICARE Region		
Mid-Atlantic	0.373[a]	0.169
Southeast	0.256	0.181
Gulf South	0.015	0.203
Heartland	0.577[b]	0.220
Southwest	0.026	0.192
Central	0.188	0.178
Southern California	0.271	0.222
Golden Gate	0.636[a]	0.298
Northwest	0.505[a]	0.253
Overseas	0.266	0.198
Branch of Service		
Air Force	-0.040	0.107
Navy/Marine Corps	-0.163	0.106
Other	-0.098	0.297
Active Duty	0.542[a]	0.244
Active Duty * Female (Interaction)	-0.794[b]	0.273
Prescription Point of Service		
Low Frequency Retail	0.179	0.109
Hi Frequency Retail	-0.139	0.138
Primary Enrollment Site		
Hospital	0.359[b]	0.125
Teaching Hospital	0.462[c]	0.118
Non-MTF Facility	0.190	0.158
Pre-treatment Comorbidity	0.044[c]	0.007
Log Transitional Migraine Expenditures	0.778[c]	0.043
Transitional MSAM Use	-0.001	0.001
Pre-Treatment Specialty Care	0.539[c]	0.108
Constant	-6.432[c]	0.654
N (subjects)	3,762	
Log-likelihood	-1,755.19	
Pseudo-R^2	0.24	

Note. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a z-test.

FIGURE 5.3. Number of Subjects by Inferior Block of Propensity Score Stratified by Cohort Status for Cross-Sectional Study Hypotheses



	0	0.05	0.1	0.2	0.3	0.4	0.5	0.55	0.6	0.8
Non User	275	231	529	450	330	206	73	51	123	9
NewUser	14	30	84	127	157	173	75	90	282	112

Nearest neighbor matching within a specified caliper was used to identify similar pairs of treated (i.e., new users) and control (i.e., non users) subjects. The caliper for the cross-sectional hypotheses was defined as 0.14162118 derived from the standard error of the propensity score distribution. Control subjects were allowed to match with a treated subject only once. Also, matching was restricted to treated subjects that had a predicted probability of treatment within the observed range of predicted probabilities for control subjects (i.e., the region of common support). This restriction excluded six treated subjects from consideration.

Caliper matching for the cross-sectional hypotheses successfully matched 73% of treated subjects resulting in 829 matched pairs. The unmatched treated patients were more likely to be younger males, on active duty. Moreover, unmatched subjects had a higher probability of receiving specialty care in the pre-treatment period, incurred greater costs for migraine related care and used significantly more migraine-specific abortive medication than did matched treated subjects.

Table 5.9 summarizes the degree of covariate balance in the 829 matched pairs for selected characteristics using standardized percent differences and two-sample t-tests. The results show that matching was successful at reducing the degree of imbalance between new and non users of daily migraine prevention. Relative reduction in standardized percent differences ranged from 61% to 99% with no statistical evidence of differences at a conventional alpha level after matching. The mean predicted probabilities (i.e., the average propensity score) to undergo treatment with daily migraine prevention before matching were 49% and 22% in the two groups. After matching, the mean predicted probabilities were within 2 percentage points indicating a high degree of balance among observed characteristics for new and non users of daily migraine prevention.

TABLE 5.9. Covariate Balance after Caliper Matching for Cross-Sectional Hypotheses on Select Characteristics (N = 1,658)

		Covariate			***Comparisons***	
Characteristic	**Sample**	**X_t**	**X_c**	**d_i**	**d_i percent reduction**	**Sig.**
Age	Unmatched	34.5	36.4	-16.5		***
	Matched	36.1	35.7	4.1	75.2	ns
Female	Unmatched	0.781	0.827	-11.6		**
	Matched	0.818	0.802	4	65.9	ns
Beneficiary Category						
Active Duty	Unmatched	0.324	0.256	15.2		***
	Matched	0.271	0.287	-3.5	77.2	ns
Treatment Facility						
Clinic	Unmatched	0.304	0.372	-14.3		***
	Matched	0.346	0.320	5.6	60.7	ns
Hospital	Unmatched	0.211	0.163	12.3		***
	Matched	0.183	0.186	-0.6	95	ns
Teaching Hospital	Unmatched	0.307	0.200	24.7		***
	Matched	0.239	0.257	-4.2	83	ns
Non-Military Facility	Unmatched	0.178	0.265	-21.1		***
	Matched	0.232	0.238	-1.5	93.1	ns
Prescription Service						
MTF Only	Unmatched	0.358	0.399	-8.5		*
	Matched	0.356	0.358	-0.5	94.2	ns
Low Retail	Unmatched	0.363	0.258	22.7		***
	Matched	0.309	0.322	-2.9	87.3	ns
High Retail	Unmatched	0.280	0.343	-13.7		***
	Matched	0.335	0.320	3.4	75.2	ns
Pre-Treatment Comorbidity	Unmatched	11.07	7.67	55.9		***
	Matched	9.51	9.73	-3.6	93.5	ns
Pre-Treatment Spending (ln)	Unmatched	6.99	5.01	105.2		***
	Matched	6.65	6.66	-0.8	99.3	ns
Pre-Treatment MSAM Use	Unmatched	39.72	22.59	33.9		***
	Matched	35.83	35.57	0.5	98.5	ns
Pre-Index Specialty Care	Unmatched	0.288	0.126	40.9		***
	Matched	0.174	0.200	-6.7	83.7	ns
Propensity Score	Unmatched	0.492	0.222	129.5		***
	Matched	0.387	0.401	-6.6	94.9	ns

Note. Geographic region and branch of service are not reported in the table but were part of the model specification and balanced after matching. d_i = standardized percent difference. X_t = new users covariate mean. X_c = non users covariate mean. Sig. = statistical significance. ns = not significant. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$, determined by a t-test.

As mentioned earlier, the matched samples for the cross-sectional and longitudinal hypotheses were similar. The primary difference between the two estimated propensity scores occurred with the standard errors. The propensity score for the longitudinal hypotheses had a larger standard error which, by definition, led to a larger caliper (i.e., the caliper was defined as 60% of the standard error). The larger caliper in the longitudinal sample led to 150 more matches (997 matched pairs vs. 847 matched pairs). Tests of balance for the longitudinal hypotheses were also satisfied (Appendix E).

Additional matched samples were generated using nearest-neighbor matching to evaluate the sensitivity of the propensity score specification. The samples generated from this matching algorithm matched more than 99% of treated subjects for both cross-sectional and longitudinal hypotheses (1,138 and 1,137 subjects respectively). However, nearest neighbor matching was unable to achieve the degree of balance observed with samples derived after caliper matching. Still, the comparison of caliper matching to nearest neighbor matching provided some insight into the sensitivity of the propensity score specification on the estimated treatment effects.

f. Estimated Effect of Exposure to Migraine Prevention on Utilization during the Post-Treatment Period

This section reports estimated measures of effect obtained from both regression and matching estimators. The results evaluated utilization outcomes

between new (exposed) and non users (not exposed) of migraine prevention during the post-treatment period in conjunction with the first six hypotheses introduced in Chapter Four. The outcomes included prescription utilization (i.e., definitely migraine related, potentially migraine related, and migraine-specific abortive medication use), health care utilization (i.e., emergent and non-emergent health care use) and total costs of migraine-related outpatient care. Each hypothesis was referred to as cross-sectional because it examined outcomes during the post-treatment interval only. Unless otherwise noted, all utilization outcomes were limited to migraine-related care.

Table 5.10 reports the least square estimates of factors affecting post-treatment expenditures and utilization, in dollars or defined daily doses (DDD). While a number of factors significantly influenced post-treatment outcomes, the results were limited to an evaluation of the effect of exposure to migraine prevention following the primary aim of the study. The other covariates were included to rule out alternative explanations for the observed effect between exposure to daily migraine prevention and the corresponding amount of health care utilization. However, the parameter estimates for control variables were not interpreted during the results.

The results in Table 5.10 showed that, after controlling for other factors, exposure to daily migraine prevention was associated with a statistically significant decline in post-treatment expenditures for definitely migraine related prescription medications (-$74.92, $P < 0.001$). Moreover, emergency room care

appeared to be less costly after exposure to migraine prevention (-$28.28, P < 0.05). On the other hand, new users of migraine prevention were associated with greater costs of non-emergent care ($65.46, P < 0.05). Neither potentially related prescription expenditures nor use of migraine-specific abortive medication were statistical different than zero after least square estimation.

A linear specification of the dependent variables on the raw scale provided a parameter estimate for daily migraine prevention (i.e., first row in Table 5.10) in the total migraine-related expenditure model (i.e., column 6) that was the sum of parameter estimates from the other expenditure models (i.e., columns 1, 2, 4, and 5). The higher costs attributed to non-emergent care coupled with cost savings from prescription medication and emergency room care led to a non-significant finding when total migraine-related expenditures were evaluated.

Each model was exposed to a battery of diagnostic tests, the results of which were summarized in Appendix F for a subset of study hypotheses. The regression diagnostics showed evidence of non-normality, heteroskedasticity, and influential data points which were expected given the earlier description of study variables. As a result, several model specifications were used to examine the robustness of the initial regression parameters from least squares estimation.

TABLE 5.10. Least Square Estimates of the Effect of Migraine Prevention on Post-Treatment Health Care Utilization

	Effect on Migraine-Related Health Care Utilization*					
Explanatory Variables	**DMR Rx ($)**	**PMR Rx ($)**	**MSAM (DDD)**	**Out Pt. Care ($)**	**Emergent Care ($)**	**Total Care ($)**
Prevention	-74.92[c]	8.71	-0.78	65.46[a]	-28.28[a]	-29.03
Age	4.35[c]	5.81[a]	0.47[c]	-2.09	-1.04[a]	7.02[c]
Female	32.98	-55.44[a]	1.11	50.55	-2.09	25.99
Mid-Atlantic	-28.74	51.79	-4.85[a]	-27.46	-16.44	-20.84
Southeast	-5.03	75.68[a]	-2.47	12.92	-4.26	79.31
Gulf South	-14.63	1.52	-3.58	-74.15	-21.90	-109.16
Heartland	83.86[a]	-12.30	-4.14	-42.77	26.24	55.03
Southwest	-32.72	88.08[a]	-2.92	-74.92	47.14	27.58
Central	-30.62	92.14[a]	-7.07[b]	-43.58	-15.50	2.44
Southern California	-15.46	151.98[c]	-3.66	12.42	21.69	170.63
Golden Gate	-26.18	22.93	-5.82	24.78	-50.61	-29.08
Northwest	9.93	50.98	0.39	-18.04	5.57	48.46
Overseas	-7.57	67.85	-0.25	27.04	41.03	128.35
Air Force	5.35	4.30	2.41	5.91	9.76	25.32
Navy/Marine	-18.00	18.68	0.28	35.45	0.58	36.71
Other	-20.36	122.55[a]	1.30	-106.22	-34.09	-38.12
Active Duty	-27.47	-50.69[a]	-4.66[b]	87.50[b]	26.09	35.44
Low Rx Retail	28.03	9.03	0.97	54.09	0.31	91.47[a]
High Rx Retail	98.13[c]	181.31[c]	0.62	-0.91	1.83	280.36[c]
Hospital	11.20	-32.97	-0.07	4.09	23.51	5.83
Teaching Hospital	-0.25	-8.33	-0.84	-69.55[a]	23.18	-54.95
Non-Military	41.80	30.92	1.87	-101.17[a]	0.57	-27.88
Co-morbid Illness	-3.62[b]	14.93[c]	0.16	6.43[b]	2.83[b]	20.57[c]
Tran HA Cost	0.14[c]	0.15[c]	2.1e^{-4}[c]	0.23[c]	0.08[c]	0.60[c]
Tran MSAM Use	2.42[c]	-0.46[a]	0.48[c]	-1.22[c]	-0.78[c]	-0.04
Specialty Care	-17.47	15.22	0.09	41.75	12.52	52.01
Constant	-148.14[c]	-322.97[c]	-7.46[c]	34.37	3.78	-432.97[c]
N (subjects)	3,762	3,762	3,762	3.762	3,762	3,762
Omnibus F-Test	69.03[c]	41.94[c]	82.89[c]	40.81[c]	17.62[c]	101.23[c]
Adjusted-R^2	0.32	0.23	0.36	0.22	0.11	0.41

Note. Outpatient care (Out Pt.) excludes expenditures incurred in the emergency room. DMR = definitely migraine related, Rx = prescription, PMR = potentially migraine related, MSAM = migraine specific abortive medication, Tran = transitional interval value. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a z-test.

Table 5.11 reports coefficient estimates of the effect of exposure to migraine prevention under a number of different model assumptions. The first two panels report results on the raw scale (i.e., dollars or defined daily doses) while the remaining panels are modeled after a natural log transformation of the dependent variable plus one (i.e., y + 1). Each model was estimated using the same set of control variables shown in Table 5.10. However, the coefficients were suppressed from the table to ease the interpretation of changes in estimated parameters for daily migraine prevention which was the focal variable of interest.

The results from Table 5.11 show that parameter estimates from a linear specification on the raw scale were sensitive to assumptions about heteroskedasticity and influential observations. Use of heteroskedasticity-consistent standard errors (Table 5.11; panel 1) changed the statistical conclusions from the previous models with only definitely migraine related prescription expenditures maintaining statistical significance ($P < 0.05$).

Identification and exclusion of influential observations using the Belsey, Kuh, and Welsh procedure (Table 5.11; panel 2) also had important implications for the study results. The coefficient estimate for definitely migraine related prescription expenditures was attenuated and no longer statistically significant while expenditures for potentially migraine related medications showed statistical evidence of cost savings after exposure to treatment (-$34.09, $P < 0.05$). In addition, the coefficient for non-emergent care was strengthened indicating that

daily migraine prevention was associated with higher costs in the post-treatment period compared to acute treatment alone ($109.12, P < 0.001).

Estimation of treatment effects after a log transformation of the dependent variables confirmed the previous results for non-emergent care expenditures (Table 5.11; panel 3). The cost of non-emergent care was 99% higher among those exposed to daily migraine prevention relative to a cohort of unexposed migraineurs (P < 0.001). However, the previous estimate of cost savings on the raw scale for potentially migraine related prescription expenditures was reversed. After log transformation, exposure to prevention was associated with 64% increase in post-treatment costs (P < 0.001). All other outcomes were no longer statistically significant. The effects estimated after log transformation of the dependent variable were robust to the presence of influential observations (Table 5.11; panel 4).

TABLE 5.11. Sensitivity of Parameter Estimates to Alternative Model Specifications for each Outcome in the Post-Treatment Period

Model Specification	***Utilization Estimates**** New Users Relative to Non Users
PANEL 1: Linear, full sample, least squares, robust standard errors	
Definitely migraine related Rx expenditures	-74.92[a]
Potentially migraine related Rx expenditures	8.71
Migraine-specific abortive medication use	-0.78
Non-emergent outpatient care expenditures	65.46
Emergent care expenditures	-28.28
Total migraine-related outpatient expenditures	-29.03
PANEL 2: Linear, trimmed sample, least squares, robust standard errors†	
Definitely migraine related Rx expenditures (n = 3,735)	-28.35
Potentially migraine related Rx expenditures (n = 3,742)	-34.09[a]
Migraine-specific abortive medication use (n = 3,742)	-1.09
Non-emergent outpatient care expenditures (n = 3,748)	109.12[c]
Emergent care expenditures (n = 3,752)	-16.71
Total migraine-related outpatient expenditures (n = 3,743)	30.60
PANEL 3: Log expenditures/MSAM use, full sample, least squares, conventional standard errors	
Definitely migraine related Rx expenditures	-0.081
Potentially migraine related Rx expenditures	0.642[c]
Migraine-specific abortive medication use	-0.041
Non-emergent outpatient care expenditures	0.992[c]
Emergent care expenditures	0.006
Total migraine-related outpatient expenditures	-0.041
PANEL 4: Log expenditures/MSAM use, trimmed sample, least squares, robust standard errors†	
Definitely migraine related Rx expenditures (n = 3,756)	-0.085
Potentially migraine related Rx expenditures (n = 3,758)	0.649[c]
Migraine-specific abortive medication use (n = 3,755)	-0.048
Non-emergent outpatient care expenditures (n = 3,760)	0.999[c]
Emergent care expenditures (n = 3,754)	0.017
Total migraine-related outpatient expenditures (n = 3,755)	-0.048

Note. Panel 3 and Panel 4 also include log transformations of the following explanatory variables: comorbidity measure, transitional migraine-related health expenditures, and transitional migraine-specific abortive medication use. Rx = prescription. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a z-test. † trimmed samples excluded influential observations based on the Belsey, Kuh, and Welsh procedure.

As an alternative to multiple linear regression, Table 5.12 reports estimates of the average treatment effect for individuals exposed to daily migraine prevention during the transitional interval. The estimates are reported in raw units (i.e., dollars or defined daily doses) for subsets of the study population matched on observable characteristics via the propensity score.

The first part of Table 5.12 reports results from the caliper matched sample. The findings suggested that remarkably similar patterns of utilization existed for the average new and non user of daily migraine prevention after matching on the observed characteristics. The only exception was non-emergent care. Mean cost of non-emergent care was $96.65 (95% CI $34.42—$158.56) higher in the post-treatment period for individuals exposed to migraine prevention. All other results from the caliper matched sample failed to reach statistical significance.

The second part of Table 5.12 presents estimated measures of effect after nearest-neighbor matching on the propensity score, a less restrictive method of matching. The results suggested that the estimated effects were sensitive to the choice of matching algorithm. In this instance, the differences in all six outcomes increased due mainly to higher average utilization among new users. This change was driven in large part by the addition of 309 (1138 – 829) unmatched treated subjects who were excluded from the previous matched sample because they did not have a control subject within the pre-defined caliper. The magnitude of observed differences was enough to reach statistical significance for four of

the six outcomes. The boost was largest for non-emergent care expenditures where the previous caliper matched estimate increased by 177% ($96.65 to $267.70) explaining a large portion of the spending increase observed in migraine-related outpatient care.

TABLE 5.12. Estimated Effect of Exposure to Migraine Prevention on Post-Treatment Health Care Utilization in a Matched Sample

	Utilization Estimates*			
Matching Algorithm	**New User**	**Non User**	**ATT**	**SE[1]**
Caliper matching without replacement†				
Definitely migraine related Rx expenditures	242.91	267.85	-24.94	22.55
Potentially migraine related Rx expenditures	274.71	297.08	-22.37	31.11
Migraine-specific abortive medication use	28.90	28.63	0.27	2.19
Non-emergent outpatient care expenditures	316.67	220.02	96.65[b]	31.59
Emergent care expenditures	45.01	69.02	-24.01	14.27
Total migraine-related outpatient expenditures	879.29	853.98	25.31	56.12
Nearest neighbor matching without replacement‡				
Definitely migraine related Rx expenditures	260.77	262.38	-1.61	21.46
Potentially migraine related Rx expenditures	352.73	275.26	77.47[a]	32.01
Migraine-specific abortive medication use	29.83	28.19	1.64	1.76
Non-emergent outpatient care expenditures	485.99	218.29	267.70[c]	35.04
Emergent care expenditures	90.46	60.21	30.25[a]	14.59
Total migraine-related outpatient expenditures	1,189.95	816.14	373.81[c]	63.03

Note. ATT = average treatment effect on the treated calculated as the difference between new and non user utilization estimates. Rx = prescription. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a t-test. [1] standard errors for the difference were computed using a bootstrap with 250 replications. † matching algorithm generated 829 matched pairs. ‡ matching algorithm generated 1,138 matched pairs.

g. Estimated Effect of Exposure to Migraine Prevention on the Change in Utilization from the Transitional to the Post-Treatment Period

Throughout this section, estimated measures of effect are reported from both regression and matching estimators. The results evaluate the change in utilization from the transitional to the post-treatment interval between new (exposed) and non users (not exposed) of migraine prevention. The goal of this section was to provide evidence for hypotheses seven through twelve introduced in Chapter Four. Utilization outcomes included prescription expenditures (i.e., definitely migraine related, potentially migraine related, and migraine-specific abortive medication use), health care expenditures (i.e., emergent and non-emergent health care use) and total expenditures of migraine-related outpatient care. Each hypothesis was longitudinal because it examined how outcomes changed over time. Unless otherwise noted, all utilization outcomes were limited to migraine-related care.

Table 5.13 presents the least square estimates of factors affecting the change expenditures and utilization from the transitional interval to the post-treatment interval. The outcomes were measured in dollars with the exception of migraine-specific abortive medication use which was measured in defined daily doses (DDD). While a variety of factors influenced these outcomes, the results were limited to an evaluation of the effect of exposure to migraine prevention on each outcome. The other covariates were included to rule out alternative explanations for the observed effect between exposure to daily migraine

prevention and the corresponding amount of health care utilization. However, the parameter estimates for control variables were not interpreted during the presentation of results.

After controlling for other factors, the results indicated that the group of subjects exposed to prevention experienced greater declines in migraine-related outpatient expenditures compared to the reference group that received abortive treatment alone (-390.72, $P < 0.001$). The majority of this decline was explained by reductions in spending on non-emergent outpatient care (-296.35, $P < 0.001$). Prescription medications identified as definitely migraine related also experienced significant declines (-$74.92, $P < 0.001$) due to a larger decrease in abortive medication utilization from the transitional to the post-treatment interval (-6.88 DDDs, $P < 0.001$).

TABLE 5.13. Least Square Estimates of the Effect of Migraine Prevention on the Change in Health Care Utilization from the Transitional to Post-Treatment Period

	Effect on Migraine-Related Health Care Utilization*					
Explanatory Variables	**DMR Rx ($)**	**PMR Rx ($)**	**MSAM (DDD)**	**Out Pt Care ($)**	**Emergent Care ($)**	**Total Care ($)**
Prevention	-61.37[c]	14.96	-6.88[c]	-296.35[c]	-47.95[c]	-390.72[c]
Age	-0.54	1.51[a]	0.10	2.91[a]	0.94	4.82[a]
Female	44.65[b]	-49.13[b]	2.12	90.37[a]	5.29	91.19
Mid-Atlantic	41.14	15.82	0.10	1.69	-5.39	53.25
Southeast	19.18	-11.39	1.98	87.15	7.90	102.83
Gulf South	27.45	-41.25	-0.51	-105.33	3.80	-115.33
Heartland	47.19	-20.18	2.84	9.93	-14.41	22.53
Southwest	49.14	33.45	4.10	8.53	-59.74[a]	31.39
Central	16.39	29.57	-2.38	-12.80	-10.18	22.99
Southern California	13.92	112.06[c]	0.77	59.04	3.58	188.60
Golden Gate	13.03	-21.04	3.06	45.50	-34.31	3.17
Northwest	22.81	42.84	8.80[a]	53.86	-38.33	81.18
Overseas	27.42	48.13	6.73[a]	68.38	38.63	182.56[a]
Air Force	23.25	20.17	3.13	-28.54	-5.77	9.12
Navy/Marine	-7.59	-2.13	0.13	9.75	15.00	15.03
Other	-12.04	5.91	0.77	-81.18	12.70	-74.61
Active Duty	-3.81	-3.12	-4.96[a]	-31.15	21.88	-16.20
Low Rx Retail	10.63	13.21	0.28	-12.03	-3.52	8.29
High Rx Retail	18.90	47.32[a]	1.04	39.84	21.15	127.20[a]
Hospital	4.97	-9.06	-0.48	-0.84	-46.66[b]	-51.59
Teaching Hospital	-7.63	-16.01	-3.70	6.87	-26.52	-43.30
Non-Military	17.81	-27.92	0.64	20.84	-16.72	-5.98
Co-morbid Illness	-0.56	1.76	-0.06	-0.20	-0.08	0.92
Pre HA Cost	0.01	0.02[b]	0.00	-0.06[c]	-0.03[c]	-0.06[b]
Pre MSAM Use	-0.18	-0.39[a]	-0.02	1.63[c]	0.37[a]	1.43[b]
Specialty Care	-45.89[b]	-29.34	-2.83	1.02	39.52[a]	-34.69
Constant	-72.34[a]	-42.89	-7.82	-255.47[b]	-31.77	-402.46[b]
N (subjects)	3,762	3,762	3,762	3.762	3,762	3,762
Omnibus F-Test	3.28[c]	2.91[c]	3.51[c]	7.22[c]	2.95[c]	6.23[c]
Adjusted-R^2	0.016	0.013	0.017	0.041	0.013	0.035

Note. Outpatient care excludes expenditures incurred in the emergency room. DMR = definitely migraine related, Rx = prescription, PMR = potentially migraine related, MSAM = migraine specific abortive medication, HA = migraine headache. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a z-test.

Moreover, spending on emergency room care showed statistically significant evidence of reductions over time in the prevention group (-$47.95, P < 0.001) compared to the control group that received acute treatment alone. In fact, the only category of expenditures that showed evidence of an increase was spending for potentially migraine-related prescription medications. However, this finding did not reach statistical significance in the least squares model ($14.96, P = 0.42).

To assess the strength of model conclusions, each least squares estimate was put through a variety of specification testing. Table 5.14 reports coefficient estimates from two of these additional regression models estimated under different model assumptions. Both model specifications were generated using the same set of explanatory variables shown in Table 5.13. However, the coefficients were suppressed from the table to ease the interpretation of changes in the main effect for daily migraine prevention, the focal variable of interest. The results were reported on the raw scale (i.e., dollars or defined daily doses) for both panels.

TABLE 5.14. Sensitivity of Parameter Estimates to Alternative Model Specifications for the Change in Health Care Utilization from the Transitional to Post-Treatment Period

Model Specification	***Utilization Estimates**** New Users Relative to Non Users
PANEL 1: Linear, full sample, least squares, robust standard errors	
Definitely migraine related Rx expenditures	-61.37[c]
Potentially migraine related Rx expenditures	14.96
Migraine-specific abortive medication use	-6.88[c]
Non-emergent outpatient care expenditures	-296.35[c]
Emergent care expenditures	-47.95[b]
Total migraine-related outpatient expenditures	-390.72[c]
PANEL 2: Linear, trimmed sample, least squares, robust standard errors†	
Definitely migraine related Rx expenditures (n = 3,746)	-59.36[c]
Potentially migraine related Rx expenditures (n = 3,753)	7.94
Migraine-specific abortive medication use (n = 3,755)	-6.60[c]
Non-emergent outpatient care expenditures (n = 3,752)	-271.82[c]
Emergent care expenditures (n = 3,759)	-47.32[b]
Total migraine-related outpatient expenditures (n = 3,747)	-380.27[c]

Note. Rx = prescription. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a z-test. † trimmed samples excluded influential observations based on the Belsey, Kuh, and Welsh procedure.

The first panel in Table 5.14 shows that the coefficient estimates from the least squares model is robust to assumptions about heteroskedasticity. Use of heteroskedasticity-consistent standard errors (Table 5.14; panel 1) did not change a single statistical conclusion from the least square estimates presented in the previous table (Table 5.13). Moreover, identification and exclusion of influential observations using the Belsey, Kuh, and Welsh procedure (Table 5.14; panel 2) had minimal implications for the results. Each estimate experienced a

slight attenuation toward the null but the statistical and qualitative conclusions remained unaltered.

As an alternative to multiple linear regression, Table 5.15 reports estimates of the average treatment effect for individuals exposed to daily migraine prevention during the transitional interval. Results are reported in raw units (i.e., dollars or defined daily doses). The estimates were generated from subsets of the study population matched on observable characteristics via the propensity score. Change in utilization from the transitional to the post-treatment interval were compared for each matched pair

The first part of Table 5.15 reports results from the caliper matched sample of 997 subject pairs. Although slightly higher in most cases, the findings from the caliper matched sample were remarkably similar to the multiple linear regression estimates reported earlier. Specifically, the results indicated that changes in utilization for migraine-related outpatient care for new and non users of daily migraine prevention were considerably different.

The results showed that mean expenditures (migraine-related) for new users declined at a greater rate ($419.28; 95% CI $299.18 – $539.39) than did similar declines in the non user cohort. This decrease was predominately attributable to a large reduction in spending for migraine-related non-emergent outpatient care ($319.49; 95% CI $235.23 – $403.75). Spending on definitely migraine related prescription medication and emergency room care also decreased at a greater rate among new users of daily migraine prevention

compared to individuals receiving acute treatment only. The only category of spending that increased in the treatment group relative to the control group was potentially migraine related prescription medication, but the result was not statistically significant ($15.28, 95% CI -$27.77 – $58.33).

TABLE 5.15. Estimated Effect of Exposure to Migraine Prevention on the Change in Health Care Utilization from the Transitional to Post-Treatment Period

	Utilization Estimates*			
Matching Algorithm	**New User**	**Non User**	**ATT**	**SE[1]**
Caliper matching without replacement†				
Definitely migraine related Rx expenditures	-87.94	-11.77	-76.17	17.27
Potentially migraine related Rx expenditures	29.14	13.85	15.28	21.86
Migraine-specific abortive medication use	-9.14	-0.24	-8.90	2.09
Non-emergent outpatient care expenditures	-388.19	-68.71	-319.49	42.78
Emergent care expenditures	-55.74	-16.83	-38.91	20.11
Total migraine-related outpatient expenditures	-502.74	-83.46	-419.28	60.98
Nearest neighbor matching without replacement‡				
Definitely migraine related Rx expenditures	-98.31	-17.72	-80.59	15.63
Potentially migraine related Rx expenditures	29.03	11.19	17.84	20.37
Migraine-specific abortive medication use	-10.01	-1.11	-8.90	1.89
Non-emergent outpatient care expenditures	-398.49	-69.19	-329.30	40.14
Emergent care expenditures	-60.37	-10.42	-49.95	18.31
Total migraine-related outpatient expenditures	-528.14	-86.14	-441.99	57.52

Note. ATT = average treatment effect on the treated calculated as the difference between new and non user utilization estimates. Rx = prescription. * a, b, and c represent p values less than 0.05, 0.01, and 0.001 respectively, determined by a t-test. [1] standard errors for the difference were computed using a bootstrap with 250 replications. † matching algorithm generated 997 matched pairs. ‡ matching algorithm generated 1,137 matched pairs.

The second part of Table 5.15 presents estimates of effect after nearest-neighbor matching on the propensity score, a less restrictive method of matching. The results suggested that the estimated effects were fairly insensitive to the choice of matching algorithm. In this instance, five of the six outcomes experienced a slight increase in the size of the point estimate obtained after caliper matching (i.e., further departure from the null hypothesis of no difference in the change in utilization between new and non users of daily migraine prevention). This insignificant change was driven by the addition of 250 additional pairs (1137 – 997) previously unmatched because no control subjects fell within the pre-defined caliper.

h. Sensitivity Analysis of Treatment Effects to Unobserved Bias

This section contains the results of a sensitivity analysis designed to assess how an unobserved factor that affected both exposure to migraine prevention and outpatient health care utilization could alter the study conclusions. It began with an evaluation of the study findings derived from the caliper matched subsets of the original migraine sample. Because propensity score matching controlled for bias due to observable factors only, it was important to consider the extent to which unobserved characteristics influence the results.

When interpreting the sensitivity results, remember that this comparison provided a worst-case scenario because it assumed that the unobserved factor was almost a perfect predictor of the outcome of interest. If the unknown factor

actually had a weaker effect on the study outcome (than perfect prediction), the conclusion would remain statistically significant at the levels of gamma reported below.

The sensitivity analysis evaluated the statistically significant results from the longitudinal study hypotheses reported in the previous section. The cross-sectional outcomes were not considered because only non-emergent care expenditures showed evidence of statistical departure from the null. All other outcomes were insignificant including the total cost of outpatient care making the sensitivity analysis irrelevant.

Table 5.16 reports the sensitivity analysis for each longitudinal outcome except potentially migraine-related prescription expenditures which was excluded because the results did not reach statistical significance. The table provided four estimates of gamma for each outcome which represent assumptions about the departure from equal treatment probabilities between matched pairs. The p-critical value characterized the most conservative estimate of statistical significance associated with each matching estimator after allowing for unequal treatment probabilities. When gamma was equivalent to one, the sensitivity analysis assumed that unobserved variable bias was absent from the results. The other three values of gamma for each outcome in Table 5.16 show the trend towards statistical insignificance. The final value of gamma represented the tipping point (i.e., the point at which the assumption about the unobserved

covariate is sufficient to reverse our statistical conclusions) for that outcome measure.

TABLE 5.16. Sensitivity Analysis of Longitudinal Hypotheses Susceptibility to Unobserved Variable Bias

	Rosenbaum Bounds	
Longitudinal Outcome Measure	**Γ (Gamma)**	**p-critical**
Definitely migraine related Rx expenditures	1.00	< 0.001
	1.35	0.007
	1.40	0.023
	1.45	0.063
Migraine-specific abortive medication use	1.00	< 0.001
	1.35	0.013
	1.40	0.042
	1.45	0.103
Non-emergent outpatient care expenditures	1.00	< 0.001
	1.70	0.013
	1.75	0.033
	1.80	0.069
Emergent care expenditures	1.00	0.003
	1.05	0.011
	1.10	0.032
	1.15	0.079
Total migraine-related outpatient expenditures	1.00	< 0.001
	1.70	0.018
	1.75	0.043
	1.80	0.088

Note. Rx = prescription.

The results from the sensitivity analysis suggested that the relative strength of study conclusions to unobserved factors varied considerably for each

outcome measure. The conclusion that emergency room expenditures declined at a greater rate among the treatment group was the most sensitive to unobserved variable bias. In this category, a gamma value of 1.15 or higher was sufficient to question the study conclusion (Table 5.16). If an unobserved covariate that almost perfectly predicted emergency room expenditures differed between matched pairs of new and non users by a factor of 1.15 or more, it would have been sufficient to reverse the study conclusions.

Spending on definitely migraine related prescription medication and utilization of abortive treatment showed similar sensitivities to unobserved variable bias. Furthermore, the conclusions for these outcomes were more robust than the previous findings about emergency room expenditures. In each case, treatment probabilities would need to have differed by a factor of more than 1.4 to change inferences about the observed treatment effect (Table 5.16). Results generated from a comparison of spending on non-emergent care and total costs of migraine-related outpatient care were the most resistant to unobserved factors (Table 5.16). Study inferences were maintained until the odds of treatment assignment differed by a factor of more than 1.75.

Chapter 6

DISCUSSION AND CONCLUSIONS

a. Discussion of Study Findings

The specific aim of this study was to determine if exposure to daily migraine prevention influenced ambulatory health care utilization compared to acute migraine treatment alone. Measures of ambulatory health care utilization included spending on prescription medication, use of migraine-specific abortive medication, spending on non-emergent medical care, and spending on emergency room care. The focal relationship between exposure to migraine prevention and corresponding health care utilization modeled the dependent variables in two ways to reflect different assumptions about the focal relationship.

The first approach compared post-treatment outcomes (i.e., the last six months of each subject's observation period) for new users of daily migraine prevention to non users who received acute treatment alone. This comparison provided a cross-sectional contrast of study outcomes in conjunction with the first set of six study hypotheses introduced in Chapter Four. The results obtained after testing these hypotheses revealed several important findings.

The most important result was that migraine-related outpatient spending in the post-treatment period was predominately uneffected by treatment with migraine prevention after controlling for pre-existing group differences. When

differences in the amount of spending were observed, the results largely provided evidence that exposure to prevention was actually associated with greater spending in the post-treatment period. For example, expenditures on non-emergent care were significantly higher among new users of migraine prevention. This finding was robust across most model specifications.

Utilization of migraine-specific abortive medication also was evaluated during the cross-sectional analysis. Each subject's use of migraine-specific abortive medication was measured in defined daily doses. The assumption was that this measure of abortive medication use provided a surrogate marker for the number of migraine headaches treated during each study interval and would provide a good measure of clinical improvement (Gaist et al., 1996; Gaist et al., 1998). Furthermore, migraine-specific abortive medication was responsible for a large majority of outpatient costs due to its expense and frequency of use. Similar to the economic findings discussed above, the amount of migraine-specific abortive medication used by individuals exposed to prevention was not significantly different than the untreated comparison group.

On the whole, the cross-sectional results showed little evidence of resource use reduction among individuals exposed to prevention compared to those subjects receiving acute treatment alone. One explanation for this conclusion was that, despite attempts to control for variation in disease severity, undetected differences remained between the two groups. This residual confounding could explain why subjects exposed to daily migraine prevention

showed higher rates of health care utilization on average. On the other hand, this finding might have been an artifact of typical medical practice whereby providers more closely follow (e.g., more office visits) patients beginning a new treatment (i.e., migraine prevention). Despite the observed difference in non-emergent care utilization, a direct comparison of all migraine-related outpatient care expenditures (i.e., prescription, non-emergent, and emergency room care) and migraine-specific abortive medication use for the cross-sectional hypotheses found no statistical evidence of an effect after adjustment for differences in observed characteristics.

Another important finding from the cross-sectional results was that the choice of model specification for both regression and matching estimators had important implications for the study results. This confirmed the conclusions of previous research that compared treatment costs from administrative claims data for other pharmaceutical treatments (Berndt et al., 2000; Russell, Berndt, Miceli, Colucci, & Grudzinski, 1999). During this analysis, the least square estimates from the cross-sectional models showed preliminary evidence of cost-savings after exposure to prevention for expenditures on definitely migraine related prescription medication and emergency room care (Table 5.10). However, these findings were reversed subsequent to the adoption of a more appropriate functional form for each regression model (Table 5.11).

A base case analysis (i.e., the best empirical model) was selected for the cross-sectional results to simplify the discussion and ease the comparison of

study results to previous work. The matching estimates from the caliper matched sample were identified as the base case analysis after a thorough review of each model and in conjunction with my a priori expectations (Table 5.12). The decision to select this estimator over competing models was based on several criteria. First, the estimated effects after caliper matching provided solid evidence of minimizing bias due to observed factors. The relative reduction in bias measured in standardized percent differences for selected characteristics ranged from 61% to 99% (Table 5.9).

Moreover, matching provided an effective way to demonstrate the comparability of the two study cohorts (i.e., new and non users of prevention) in an easily interpretable format. The histogram of treatment probabilities stratified by both the inferior block of the propensity score and cohort membership clearly depicted the small number of counterfactual comparisons for treated subjects at the upper end of the propensity score distribution (Table 5.3). In other words, at a certain point along the continuum of treatment probabilities, almost everyone received treatment explaining why only 73% of the treated subjects from the cross-sectional models were matched. The remaining individuals exposed to treatment lacked an appropriate match in the comparison group to estimate what would have happened to those individuals in the absence of treatment. This distinction was important for observational research and not easily observable with regression. Furthermore, regression results could have been misleading in this instance because the values for comparison subjects at the upper end of

propensity score distribution were inferred or extrapolated from existing patterns in the data rather than actual observations.

Nonetheless, it is still an open debate about whether or not matching outperformed more traditional estimates obtained from regression (Sturmer et al., 2006). The biggest limitation of matching in this study was the exclusion of subjects from the estimated effect of treatment (1,658 in caliper matched estimates versus 3,762 subjects in the full regression models). As a result, the matching estimates sacrificed some precision. Also, exclusion of study subjects raised concerns about generalizeability because it eliminated treated subjects at the upper end of the propensity score distribution. Although, this is arguably less of an issue because a policy initiative to increase use of migraine prevention would most likely target those individuals whose indication for treatment is less certain (i.e., at the lower end of the propensity score distribution). Despite these limitations, I believe that the caliper matched results still provided the best estimate of the true cross-sectional association between exposure to prevention and post-treatment spending.

In contrast to the cross-sectional results, a second method was used to estimate the effect of daily migraine prevention on resource utilization in the Military Health System. This second method differed primarily in its treatment of the dependent variables. It evaluated the change in utilization over time from the transitional to post-treatment period for new and non users of prevention. As a result, this method included more longitudinal information and was consistent

with the remaining six study hypotheses. The analyses calculated the effect of exposure to migraine prevention and compared the outcome to the counterfactual scenario obtained from the matched comparison group (i.e., what would have happened to the treatment group in the absence of treatment).

The results from the longitudinal analysis showed that exposure to daily migraine prevention was associated with greater declines in migraine-related outpatient expenditures than what would have been expected if the new users had not been exposed to prevention. The biggest declines were observed for non-emergent outpatient care expenditures followed closely by spending on definitely migraine related prescription medication. Together, these two categories were responsible for roughly 91% of the reduction in spending on migraine-related health care treatment.

One explanation for this result was that exposure to daily migraine prevention reduced the frequency and severity of migraine headaches leading directly to a reduction in health care utilization. The inability to observe this association in the cross-sectional analysis could have occurred for several reasons. For instance, daily migraine prevention was likely prescribed preferentially to patients with more debilitating disease. This phenomenon has been reported previously with migraine prevention and would be appropriate based on current therapeutic recommendations (Ramadan et al., 2000; Snow, Weiss, Wall, & Mottur-Pilson, 2002). If use of migraine-specific abortive medication was a reliable and valid surrogate for the number of actual migraine

headaches experienced, this conclusion was supported. New users, on average, received more abortive medication before exposure to prevention and consumed lesser amounts of abortive treatment after initiation of a preventive medication than did the comparison group of non users. This accounted for the finding of reduced spending on medication classified as definitely related to migraine.

However, not all study results from the longitudinal hypotheses supported the conclusion that daily migraine prevention consistently reduced the use of health care resources. Spending on medication that was potentially related to migraine increased in the new user group after exposure to prevention. Potentially related medication included drugs that could be used in the management of migraine but also had other indications making it impossible to determine with any certainty that the drugs were used solely for migraine. Drugs in this category included pain medication (e.g., NSAIDS or opioid-containing products) or anti-emetics. This category also included the drugs used for migraine prevention because each preventive medication had more than one indication for treatment. The assumption was that even if a patient in the new user cohort did not receive the drug initially for migraine prevention, they would still receive the benefit of treatment (i.e., therapeutic doses for prevention are often lower than for other indications). Thus, it was not surprising that the new user cohort increased relative to the non users of prevention for spending on potentially migraine related medication. Cost of prevention continues to be an important factor in the treatment decision because the high cost of several

preventive medications makes them cost-ineffective for all but the sickest patients (Adelman, Adelman, & Von Seggern, 2002; Adelman, Brod, Von Seggern, Mannix, & Rapoport, 1998).

Another interesting finding from the longitudinal analysis was that the results were much more robust to choice of model specification compared to the previous estimates from the cross-sectional analysis. Consistency was observed for both regression and matching estimators. The results from the longitudinal analysis were, in general, less sensitive to assumptions about the data. However, the longitudinal models were unable to explain as much variance in the outcome measure. The longitudinal regression models explanatory power ranged from 1% to 4% suggesting that other unobserved factors also play an important part in the process of change (Table 5.13).

As mentioned earlier, the primary difference between the cross-sectional and longitudinal analysis was the specification of the dependent variables. In the longitudinal analysis, each outcome was modeled as a difference (i.e., the transitional outcome subtracted from the post-treatment outcome). When combined with propensity score methods, the longitudinal analysis provided what was essentially a matching adjusted difference-in-differences (DiD) model. The primary advantage of this approach was that it accounted for pre-existing group differences and provided some measure of control for time-invariant unobserved factors (Allison, 1990). Additionally, empirical work has shown that this method

outperformed several other propensity score estimators based on its ability to minimize bias (Heckman et al., 1997).

Conclusions from both analyses were founded on the assumption of ignorable treatment assignment or selection on observables which is implicit when estimating the average treatment effect among the treated with propensity score models; an untestable assumption. However, general consensus is that this assumption is difficult to support with information acquired from administrative claims data (Motheral et al., 2003). Thus, a sensitivity analysis was conducted to judge how unobserved covariates might influence the inferences from the study.

The findings from the sensitivity analysis provided important insight into the strength of conclusions for the longitudinal analysis which concluded that exposure to prevention was associated with a greater rate of decline in expenditures than what would have occurred in the absence of treatment. Results from the sensitivity analysis suggested that to reverse the longitudinal study results, an unobserved covariate would need to increase the odds of exposure to prevention by a factor of 1.8 or more within each matched pair.

To put this in perspective, individuals that received specialty care during the pre-treatment period experienced an increase in the odds of exposure to prevention by a roughly factor of 1.7 relative to those who did not receive specialty care (Table 5.8). Thus, a binary covariate slightly stronger than receipt of pre-treatment specialty care would be sufficient to alter the statistical

conclusions (i.e., p-values all greater than 0.05). This does not mean that exposure to daily migraine prevention had no effect. Instead, it meant that the presence of a hypothetical unobserved binary covariate that changed the odds of exposure by more than a factor of 1.8 would result in confidence intervals for each measure of effect that included zero.

Despite the usefulness of considering unobserved bias in observational studies, this method was not without its own limitations (Rosenbaum, 2002). First and most importantly, the sensitivity analysis could not determine whether or not these biases were actually present. Furthermore, the analysis assumed that the hypothetical unobserved variable had an almost perfect relationship with the outcome of interest. Due to the complexity associated with modeling health care expenditures, the chance that such a variable actually existed was slim. With this in mind, the sensitivity analysis provided what should be thought of as a worse case scenario. In truth, if you could modify the assumptions about the unobserved variable so that it had less than a perfect relationship with the outcome of interest, the result would show that study conclusions were more robust to larger departures from equal treatment probabilities (i.e., gamma greater than 1.8) within matched pairs. This limitation remains an area that deserves further consideration with the hope that a sensitivity analysis can be employed in the future to more accurately represent real world conditions.

b. Interpretation of Results in Context of Previous Research

The results from this study are somewhat different than previous research that has evaluated the relationship between exposure to migraine prevention and health care utilization (Etemead et al., 2005; Silberstein et al., 2003). It provided a useful context for interpretation of the results obtained during this analysis. The remainder of this section contrasts the results from this study to the conclusions of previous work, highlights some similarities, and proposes some explanations for the observed discrepancies.

The first researchers to publish a study on the relationship between daily migraine prevention and health care utilization were Silberstein and colleagues (2003). Their study was conducted with data from the LifeLink^{TM} Integrated Claims Database and employed a one group pretest-posttest design of patients exposed to prevention. Each patient was followed over 18 months (6 months prior to exposure and 12 months after). The results showed that prevention reduced the use of other migraine medications as well as visits to physician and the emergency room (Silberstein et al., 2003).

Both this dissertation and the Silberstein et al. (2003) study employed similar methodological designs. However, the results from this study were able to strengthen the work by Silberstein et al. by addressing some of the shortcomings in their paper that were used to criticize the results after publication (Adelman et al., 2003). The authors were criticized principally because they were unable to rule out alterative explanations for the observed treatment effect

such as the well-documented phenomenon of regression to the mean. Moreover, they did not include the costs of prevention when considering total costs of migraine related care. In contrast, this dissertation made use of a comparison group matched on all observable characteristics which increased the strength of study conclusions to threats against validity such as regression to the mean (Shadish, Cook, & Campbell, 2002). Moreover, the cost of daily migraine prevention was considered during the analysis. Interestingly, even after the improvements in methodological design the qualitative results from the two studies were essentially identical.

The results reported by Etemead et al., (2005) differed somewhat from the results reported in this study. The Etemead paper examined the costs of migraine-related health care services in moderate-to-severe migraine patients treated with daily migraine prevention. Results were obtained from a retrospective cohort design of claims data and incorporated a comparison group of patients with migraine who were not exposed to prevention. Etemead et al. concluded that migraine prevention generated cost-savings compared to acute treatment alone and any intervention that might cost less than the projected savings (i.e., $559.71 per person per year) should be considered if it effectively increased the use of migraine prevention.

The conclusion by Etemead et al. (2005) that daily migraine prevention resulted in cost-savings relative to acute treatment alone was not supported by this study. The evidence against this conclusion can be observed during from

the results obtained after the cross-sectional analysis. The results suggested that exposure to prevention resulted in either more costly care (e.g., non-emergent ambulatory care) or made no difference whatsoever on migraine related health care spending (e.g., definitely migraine related prescription expenditures). Had daily migraine prevention resulted in cost-savings compared to acute treatment alone, the cross-sectional results would have shown a negative and statistically significant difference between the two study cohorts in favor of prevention.

A variety of explanations could account for this discrepancy between the two studies. For instance, they evaluated different patient populations. It is possible that military beneficiaries varied in unknown ways from a more traditional insured population in the United States. In addition, the cost of medical care and prescription medication are traditionally less expensive in the military compared to commercially available prices for health care. Also, the post-treatment follow-up times were different (i.e., six months versus one year) leaving open the possibility that the effect of prevention did not have sufficient time to mature during this study. While all are plausible explanations, the best justification for the observed discrepancy between the two studies could be explained by the different methods used to identify the study comparison group.

As previously discussed, Etemead et al. (2005) selected individuals with migraine that did not receive preventive treatment but were required to possess at least 18 triptan equivalents during the first six months of the post-treatment

period. They placed no such requirement on the treatment group who was exposed to prevention. This was important distinction because prescription costs were the most expensive category of care during their study accounting for 88% of post-treatment spending (Etemead et al.). Moreover, the prescription costs in their study were driven primarily by triptans; a costly medication class available for the treatment of migraine. Thus, the conclusion that the treatment group was less expensive than the comparison group could probably be better explained as a selection issue rather than an effect of exposure to treatment (i.e., daily migraine prevention). In other words, they selected only the most expensive non users of prevention to serve as the comparison group.

To circumvent this selection issue, researchers must avoid choosing comparison subjects based on the post-treatment outcomes that are being evaluated during the study. If Etemead et al. (2005) had done this, the results would probably have been similar to the cross-sectional conclusions reported from this study; patients exposed to prevention did not consume fewer resources than did a comparison group of subjects receiving acute treatment alone. At best, there was no difference and within some categories, individuals exposed to prevention consumed more resources than the untreated comparison group (e.g., non-emergent ambulatory care).

Clinically, this conclusion should have more intuitive appeal because in actual practice, daily migraine prevention is generally reserved for patients with more frequent or disabling migraine headaches (Snow et al., 2002; Ramadan et

al., 2000). Research has shown that a small number of migraineurs with frequent headaches account for a disproportionate share of disease related health care utilization (Joish, Cady, & Shaw, 2000; Stang et al., 2004). Incidentally, these are the same patients that will most likely be candidates for treatment with prevention. As a result, patients exposed to daily migraine prevention in an observational setting should almost certainly consume more health resources than would the typical migraine patient who was not exposed to prevention.

The cross-sectional hypotheses addressed the question of whether patients who had identical levels of health care utilization prior to treatment with prevention would consume different amounts of health care during the post-treatment interval. In terms of total ambulatory health care spending, the answer is they probably would not; patients starting from an equal footing during the transitional interval would have consumed similar amounts of resources during the post-treatment period, regardless of exposure to prevention.

However, new users exposed to prevention actually utilized significantly more health resources while starting treatment than did the non users from the comparison group. The cross-sectional analysis assumption that the two groups start at the same level of health care utilization prior to treatment exposure was unrealistic. While the cross-sectional results attempted to control for baseline characteristics, it appeared to under adjust for the pre-existing differences

between the two study groups. This phenomenon has been reported previously (Lord, 1967, 1969).

As a result, it was important to examine whether subjects exposed to treatment changed over time after initiation of daily migraine prevention. The results reported from the longitudinal analysis were able to address this question and account for pre-existing group differences by modeling the outcome as the change over time during the transitional and post-treatment period (Allison, 1990). As previously discussed, the results showed that exposed patients were less costly than what would have been expected in the absence of exposure for treated subjects. However, at no time were exposed subjects less costly than the untreated comparison group as might be expected when evaluating the effect of treatment in the absence of random assignment.

c. Usefulness and Implications of Study Findings

The results and conclusions are useful to a variety of individuals responsible for the delivery of health care to patients suffering from migraine headache. In both the Department of Defense (DoD) and the Military Health System (MHS) this group is made up of a range of personnel including health care providers, researchers, and policy makers. Each stakeholder's interest in the results is summarized below. This is section ends with a discussion of how the study findings fit into a broader context of migraine management and treatment in the United States.

Health care providers in the Military Health System are a logical recipient for the study results. This group of providers includes a wide range of specialties beyond just physicians. Pharmacists, physician-extenders, nurses, and other ancillary health personnel can all apply information obtained from the study to their respective practice. For instance, the study described the characteristics of patients with migraine in the Military Health System. As expected, the disease predominately affected women in their mid to late thirties and was consistent across each branch of service. In addition, one out of every four patients studied was an active-duty military member dispelling the perception that migraine does not effect our men and women in uniform. This information is important for screening high risk patients and targeting migraine-related interventions toward appropriate individuals.

In addition to describing the characteristics of patients with migraine, the study provided more detailed data about the treatment of migraine within the Military Health System (MHS). This information was useful because it provided an assessment of how well the MHS managed drug therapy choices for patients during the time period studied. Among new users of prevention, only 60% received a group one preventive medication (i.e., those medications with the greatest evidence of efficacy for prevention of migraine). This finding suggested that providers starting patients on daily migraine prevention could make improvements on initial prescribing choices for daily migraine prevention. Proactive pharmacists and educational initiatives that target providers are two

effective methods for increasing evidenced-based prescribing for the treatment of common health care conditions (Avorn & Soumerai, 1983; Schaffner, Ray, Federspiel, & Miller, 1983; Soumerai & Avorn, 1986).

Health researchers in the DoD are another group that can benefit from the study results. The dissertation offered more than just new information about the management of migraine. It also provided a practical application of effectiveness-based research using military administrative claims data. This type of study has immense potential to assist decision-makers in the Department of Defense. However, because patients self-select into treatment groups and administrative data does not measure all important confounders, doubt about study conclusions will remain (McMahon, 2003). Despite the limitations, the importance of research using observational data has begun to be recognized by other federal agencies.

Recently, AHRQ (2005) published a press release announcing 13 new federally funded centers designed to develop evidence and inform decisions about effectiveness (referred to as DEcIDE centers). The centers were created to answer questions about the use, benefits, and risks of medication derived from effectiveness-based research studies. The Military Health System could benefit by partnering with the new centers and applying effectiveness-based research methods to research questions of interest to the Department of Defense (DoD). Health researchers in the DoD will need to take the lead on this and insure that the benefits are effectively communicated to decision-makers.

Health researchers could also benefit from increased awareness about methods to reduce remaining uncertainty attributable to unobserved factors; an area that is currently the object of intense debate in the scientific community. Two of the more promising strategies were incorporated in this study to counter this often cited flaw. First, the study employed a new-user cohort design. Previous work has argued that a new-user design can eliminate bias from several sources including the effect of time on the study outcome measures and the effect of drug exposure on the covariates proposed to control for pre-existing group differences (Ray, 2003). The new user design reduces these biases by identification and exclusion of all the prevalent users of daily migraine prevention leaving only the individuals who were under observation prior to beginning the treatment of interest.

The study also conducted a sensitivity analysis of conclusions designed to examine the strength of the results to unobserved variable bias using a method outlined by Rosenbaum (2002). Sensitivity analysis is gaining popularity in the health care literature but is still utilized infrequently. In this instance, the effect of one hypothetical binary covariate was considered on each statistically significant study result. Methods of sensitivity analysis are being studied and improved on a regular basis. For example, recently some researchers have proposed using external information or propensity score calibration from validation data to estimate the effect of multiple unobserved confounders in database studies (Schneeweiss, Glynn, Tsai, Avorn, & Solomon, 2005; Sturmer, Schneeweiss,

Avorn, & Glynn, 2005). This area of research holds great promise for reducing concerns about confounding. As effectiveness-based research continues to inform policy decisions in the Military Health System, researchers should work to include both new user designs and sensitivity analyses into their arsenal of research methods.

Health policy makers in the Military Health System are the last group of stakeholders that should make use of the study results. At least two major findings had implications for health policy in the Department of Defense. The first was that patients with migraine in the MHS consumed significantly more outpatient resources than did the average patient enrolled in TRICARE. Spending on outpatient health care for the initial migraine sample population was estimated at $6,941 per person per year (Table 5.2). In comparison, the average TRICARE beneficiary spent only $3,261 per person per year over the same time period (Woskow, 2004). This difference represents more than a two fold increase in outpatient spending among patients with migraine in the Military Health System. Migraine-related care was a significant part of this spending accounting for over one-third of all outpatient expenditures (Table 5.2). As a result, an effective policy directed toward patients with migraine has the potential to realize significant cost-savings in the Military Health System.

The second finding that had implications for health policy in the Department of Defense was that exposure to daily migraine prevention led to cost avoidance relative to what the treated patients would have spent in the

absence of prevention. For instance, the estimate from the caliper matched sample suggested that exposure to prevention led to roughly $347,000 ($419 * 829 subjects) in savings for the treated patients (Table 5.15). Individuals treated with prevention were not less costly than the average migraineur receiving acute treatment alone. However, prevention still lead to net plan savings for patients exposed to treatment with prevention because they spent less than they would have without treatment. Thus, an intervention that increased the appropriate use of daily migraine prevention could effectively substitute less expensive pharmaceutical treatments for other more costly types of outpatient care.

The policy relevance of this study goes beyond just simple cost-savings. Some of the information used during this dissertation might also be advantageous to consider for the development of claims-based quality indicators of appropriate drug use among patients with migraine in the Military Health System. The data could easily come from the military's extensive prescription claims database. Earlier research has recommended several therapeutic quality indicators for drug therapy but nothing that specifically addressed the treatment of migraine (McColl, Roderick, Gabbay, Smith, & Moore, 1998; Wenger, & Shekelle, 2001).

Many opportunities exist to develop claims-based quality indicators of migraine-related drug therapy. The information would describe current trends of treatment and target individuals most likely to benefit from prevention. For example, the number of patients receiving prevention among all migraine

patients stratified by use of migraine-specific abortive medication per month could be useful as a quality indicator. Another example of a useful quality indicator is the number of patients receiving a group one preventive medication for daily migraine prevention among all patients exposed to prevention. This indicator would be indicative of evidence-based practices and cost-effective prescribing. Finally, patient adherence with prevention could be assessed using a common measure such as the proportion of days covered during the first six months following treatment initiation. This is an area where pharmacists should play a critical role. Direct interventions to enhance adherence through patient education and monitoring of treatment are critical because patients will not reap the benefits of treatment if they are unable to take the prescribed medication as directed.

The examples described above include just a few of the potential quality indicators available for the treatment of migraine. Moreover, this could easily be expanded to other significant health care conditions plagued by sub-optimal treatment. Extending the use of administrative claims data in the Military Health System is an important first step toward real-time monitoring of treatment quality. The data will be essential as we strive to understand current treatment patterns, identify areas for improvement, develop appropriate interventions to address deficiencies, and monitor outcomes. It is an area that policy makers in the Department of Defense must address.

Although this study was limited to patients in the Military Health System, it is useful to consider the results in a broader context of migraine management within the United States. Previous research has shown that patients with migraine headache do not routinely consult physicians for treatment and when they do seek medical care the condition is frequently misdiagnosed (Lipton, Diamond et al., 2001; Lipton et al., 1992). Moreover, treatment patterns with prescription medication in the United States suggest that the current prescribing practices are sub-optimal and could be improved (Devine, Hadsall, & Farley, 2005).

This is particularly true about previous research that examined treatment with daily migraine prevention; a finding that has unique relevance to the specific aim of this dissertation. The results from the American Migraine Study II showed that one-forth of surveyed subjects had more than three migraines monthly and over one-half of all subjects reported severe impairment from their headaches (Lipton, Stewart et al., 2001; Lipton, Scher et al., 2002). Yet, less than 5% of patients surveyed were receiving treatment with daily migraine prevention (Lipton, Diamond et al., 2001).

This result provides convincing evidence that treatment with daily migraine prevention is under-utilized in the United States. Although appropriate use of prevention was not evaluated directly during this study, there is little evidence to suggest that the Military Health System does a better job initiating daily migraine prevention for appropriate patients. The efficacy of prevention has been

established (Ramadan et al., 2000; Snow et al., 2002). Moreover, the results from this study and previous work have shown that prevention can influence migraine-related resource utilization (Silberstein et al., 2003). In addition, research demonstrated that prevention could positively impact health-related quality of life and activities of daily living (D'Amico et al., 2006). Thus, improving inappropriate prescribing with daily migraine prevention should be a priority in the management of migraine.

d. Strengths and Limitations of the Study

The design and analysis of this study included both some strengths and limitations. A strength of this study included the large sample size of patients with migraine in the Military Health System. Based on the a priori power analysis, the study included a sufficient number of subjects to detect a medium effect at the 0.05 level even after the new user design and matched analysis excluded a number of participants. Also, the study was conducted with patients that were treated in a usual care setting. This provided a more practical evaluation of migraine prevention in a traditional practice environment. Furthermore, it avoided some of the biases that can occur in a randomized clinical trial attributable to the intense follow-up and control that these studies employ. As a result, conclusions from a randomized trial may not be generalizeable to patients who will actually receive daily migraine prevention.

The study made use of an analysis plan that estimated treatment effects in the presence of common difficulties associated with observational research designs. The plan included a new user design with matched and regression analyses. In addition, the sensitivity analysis considered how inferences might have changed under different assumptions about biases from unobserved factors. While no fix could be proven with certainty, the analysis plan did allow for a comparison of treatment effects across a variety of model assumptions. This strengthened the study conclusions for those effects that were robust across multiple model specifications.

The final strength of this study was its relative cost-effectiveness. It was completed for a fraction of the expense of other potential study designs. Prospective cohort studies or randomized clinical trials would have required a great deal more money and manpower to conduct for a similar sized sample of patients with migraine. In comparison, this retrospective analysis of claims data was completed by a much smaller number of researchers and was finished over a shorter time interval because the data had already been collected.

This research project also had several important limitations. The first was an inability to control treatment assignment which is a common limitation of retrospective claims analyses. As a result, it is possible that the reported treatment effects were due to unobserved characteristics rather than exposure to daily migraine prevention. Considerable time and effort were taken during the

design and analysis of the study to account for this limitation. However, it remained an untestable assumption making it impossible to rule out completely.

Another limitation of the study was the absence of some important explanatory variables known to influence health care utilization. For example, disease severity and detailed measures of sociodemographic characteristics such as income or education were not available in claims databases maintained by the Military Health System. As a result, the study explanatory variables had to be limited to the available ones.

Where possible, the study employed proxy measures for unobserved variables. For instance, in place of disease severity the study used a measure that reflected use of migraine-specific abortive medication in defined daily doses. This measure was an approximation of the number of headaches a patient experienced and thereby, served as an indicator of disease severity. Defined daily doses have been used previously in database analyses of patients with migraine (Gaist et al., 1996; Gaist et al., 1998). Still, collection of extra data could enhance our understanding of how a patient decides to use health care resources for migraine.

An additional limitation of this study was the exclusion of indirect costs which are known to be a significant burden in migraine. Indirect costs (e.g., cost of diminished productivity in the workplace) are greatest among individuals with frequent or severe migraine headaches (Stewart et al., 2003). Furthermore, daily migraine prevention has been shown to reduce the frequency and severity of

migraine headaches (Ramadan et al., 2000; Snow et al., 2002). Based on this information, it seemed reasonable to assume that daily migraine prevention might also influence indirect costs secondary to migraine. As a result, the conclusions reported during this study more than likely provide a conservative estimate of the true net economic impact associated with initiation of daily migraine prevention.

Generalizeability of the study results to populations beyond the Military Health System is another potential limitation. The descriptive data about subjects with migraine in the military system showed a great deal of agreement with previous epidemiological research (Lipton, Scher et al., 2002). However, other unique aspects of military medicine may have influenced the patients' response to daily migraine prevention. For example, many military members have first-dollar health care coverage (Galvin, 2005). Those military beneficiaries who do share in the cost of their health care typically pay less than the average person with employer-sponsored health coverage (Galvin, 2005). This could have resulted in larger treatment effects because patients in the Military Health System used more resources before exposure to daily migraine prevention. If treatment was applied to a more traditional employer-sponsored health plan with higher levels of patient cost-sharing, the results could be significantly different. Until additional information is available, generalizing the results to other populations should be undertaken cautiously.

A further limitation of the study was the censored observation time. Each subject had 18 months of follow-up that included 6 months before the index date and 12 months after. Exposure to migraine prevention occurred during a 6 month interval beginning on the index date. It is possible that following the patients over a longer time horizon could have important implications for study results. However, this was believed to be unlikely because migraine headaches are generally considered to be intermittent with a great deal of variation in headache intensity. As a result, post-treatment follow-up time between 6 and 12 months was thought to be sufficient.

Finally, errors in coding are problematic and difficult to assess in claims data. During this research, the assumption was made that military data were accurate because there are criminal penalties for over reporting care. Furthermore, underreporting would have adversely affected each clinics manpower authorization and reduced revenues in clinics outside of the military. Thus, providers and clinics alike had a strong incentive to report this information accurately. In addition, several quality checks (i.e., missing or out of range values) were performed during the data analysis to look for any unusual observations. The results from the quality checks suggested that the data was appropriate for use during the analysis.

e. Directions for Future Research

The conclusions from this study highlight at least four additional areas for further research. First, prospective studies should be undertaken to confirm the results obtained from the earlier observational research. This does not necessarily require that a study be designed solely for the purpose of assessing the economic outcomes after treatment with daily migraine prevention. Recently, several new products have received FDA approval for migraine prevention (e.g., divalproex sodium or topiramate). Economic analysis along side the clinical trials conducted during the approval process could help confirm the results of this research.

Although less likely to be funded, studies comparing older and less expensive medication (i.e., propranolol or amitriptyline) to newer products (i.e., divalproex sodium or topiramate) for prevention would be extremely useful when making decisions about treatment. Because of the large number of preventive treatments, many with different mechanisms of action, it is likely that migraine preventive medications differ on important drug related factors such as safety, cost, and ease of dosing/administration. As such, active comparator trials with daily migraine prevention could help identify important factors to consider with migraine prevention and improve providers' ability to make more effective treatment decisions.

In addition to prospective studies, economic outcomes should be expanded to include indirect costs. Humanistic outcomes should also be

considered when assessing the value of daily migraine prevention. One of the first published prospective studies to report on humanistic outcomes for this treatment argued that it improved health-related quality of life and reduced migraine-related disability (D'Amico et al., 2006). However, the study was small in scale and should be replicated to determine if the benefits of prevention persist across patient populations and for other drugs thought to be effective for this indication.

Additional methodological exploration also is needed to improve the results of effectiveness-based research on administrative claims data. For example, empirical work to strengthen existing methods that adjust for unmeasured confounders in observational studies would greatly enhance causal inquiry from retrospective analyses of large data sets. Moreover, the Department of Defense should invest resources to do a thorough evaluation of the validity and reliability of the Military Health Systems (MHS) claims data. During this study, the assumption was made that data was useful in the absence of published evidence. However, the ability to cite empirical research from peer-reviewed sources about the reliability and validity of the data would strengthen conclusions from studies based on this data.

f. Study Conclusions

The study results indicate that exposure to daily migraine prevention did effect ambulatory health care utilization in the Military Health System compared

to acute migraine treatment alone. Treatment with prevention resulted in lower rates of utilization relative to what new users of prevention would have consumed in the absence of treatment. Moreover, the lower rate of migraine-related utilization in the Military Health System corresponded to a $347,000 reduction in spending among patients exposed to daily migraine prevention. The value of prevention appears to extend beyond just clinical improvement to include economic benefits as well. While the use of prevention remains a patient specific decision, only a small fraction of migraineurs who could benefit from prevention are actually receiving it. Increasing the appropriate use of daily migraine prevention will require that health care providers understand the indications for prevention and are clear about which medications are most suitable for treatment. Furthermore, health policies should encourage candid discussions between health care providers and patients that account for individual preferences and focus on the benefits and risks of treatment. These modest improvements are a first step toward bettering medical care for patients with migraine and enhancing the appropriate utilization of daily migraine prevention.

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Appendix A

CLASSIFICATION OF DEFINITELY AND POTENTIALLY MIGRAINE RELATED MEDICATION

Generic Name	Classification
ALMOTRIPTAN MALATE	Definitely related to migraine
DIHYDROERGOTAMINE MESYLATE	Definitely related to migraine
ELETRIPTAN HYDROBROMIDE	Definitely related to migraine
ERGOCALCIFEROL	Definitely related to migraine
ERGOLOID MESYLATES	Definitely related to migraine
ERGOT TT/CAFF/BELL ALK/P-BARB	Definitely related to migraine
ERGOTAMINE TART/BELLAD ALK/PB	Definitely related to migraine
ERGOTAMINE TARTRATE	Definitely related to migraine
ERGOTAMINE TARTRATE/CAFFEINE	Definitely related to migraine
FROVATRIPTAN SUCCINATE	Definitely related to migraine
ISOMETHEPTENE/APAP/DICHLPHEN	Definitely related to migraine
NARATRIPTAN HCL	Definitely related to migraine
RIZATRIPTAN BENZOATE	Definitely related to migraine
SUMATRIPTAN	Definitely related to migraine
SUMATRIPTAN SUCCINATE	Definitely related to migraine
ZOLMITRIPTAN	Definitely related to migraine
ACEBUTOLOL HCL	Potentially related to migraine
ACETAMINOPHEN	Potentially related to migraine
ACETAMINOPHEN/BUTALBITAL	Potentially related to migraine
ACETAMINOPHEN/CAFFEINE/BUTALB	Potentially related to migraine
ALFENTANIL HCL	Potentially related to migraine
AMITRIP HCL/CHLORDIAZEPOXIDE	Potentially related to migraine
AMITRIPTYLINE HCL	Potentially related to migraine
AMITRIPTYLINE HCL/PERPHENAZINE	Potentially related to migraine
ASPIRIN	Potentially related to migraine
ASPIRIN/CAFFEINE/BUTALBITAL	Potentially related to migraine
ASPIRIN/MEPROBAMATE	Potentially related to migraine
ATENOLOL	Potentially related to migraine
ATENOLOL/CHLORTHALIDONE	Potentially related to migraine
BOTULINUM TOXIN TYPE A	Potentially related to migraine
BUPROPION HCL	Potentially related to migraine
BUTORPHANOL TARTRATE	Potentially related to migraine
CARISOPRODOL	Potentially related to migraine
CARISOPRODOL/ASPIRIN	Potentially related to migraine
CELECOXIB	Potentially related to migraine

Generic Name	Classification
CITALOPRAM HYDROBROMIDE	Potentially related to migraine
CLONIDINE HCL	Potentially related to migraine
CODEINE PHOS	Potentially related to migraine
CODEINE PHOS/ACETAMINOPHEN	Potentially related to migraine
CODEINE PHOS/CARISOPRODOL/ASA	Potentially related to migraine
CODEINE SULF	Potentially related to migraine
CODEINE/APAP/CAFFEIN/BUTALB	Potentially related to migraine
CODEINE/ASA/CAFFEINE/BUTALB	Potentially related to migraine
CYCLOBENZAPRINE HCL	Potentially related to migraine
CYPROHEPTADINE HCL	Potentially related to migraine
DESIPRAMINE HCL	Potentially related to migraine
DHCODEINE BT/ACETAMINOPHN/CAFF	Potentially related to migraine
DICLOFENAC POTASSIUM	Potentially related to migraine
DICLOFENAC SODIUM	Potentially related to migraine
DICLOFENAC SODIUM/MISOPROSTOL	Potentially related to migraine
DIFLUNISAL	Potentially related to migraine
DIHYDROCODEINE/ASPIRIN/CAFFEIN	Potentially related to migraine
DILTIAZEM HCL	Potentially related to migraine
DIVALPROEX SODIUM	Potentially related to migraine
DOXEPIN HCL	Potentially related to migraine
DULOXETINE HCL	Potentially related to migraine
ESCITALOPRAM OXALATE	Potentially related to migraine
ETODOLAC	Potentially related to migraine
FENOPROFEN CALCIUM	Potentially related to migraine
FENTANYL	Potentially related to migraine
FENTANYL CITRATE	Potentially related to migraine
FENTANYL CITRATE/PF	Potentially related to migraine
FLUOXETINE HCL	Potentially related to migraine
FLURBIPROFEN	Potentially related to migraine
FLURBIPROFEN SODIUM	Potentially related to migraine
FLUVOXAMINE MALEATE	Potentially related to migraine
GABAPENTIN	Potentially related to migraine
GUANFACINE HCL	Potentially related to migraine
HYDROCODONE BIT/ACETAMINOPHEN	Potentially related to migraine
HYDROCODONE BIT/HOMATROPINE	Potentially related to migraine
HYDROCODONE/CHLORPHEN POLIS	Potentially related to migraine
HYDROMORPHONE HCL	Potentially related to migraine
IBUPROFEN	Potentially related to migraine
IBUPROFEN/HYDROCODONE BIT	Potentially related to migraine
IMIPRAMINE HCL	Potentially related to migraine
IMIPRAMINE PAMOATE	Potentially related to migraine
INDOMETHACIN	Potentially related to migraine
KETOPROFEN	Potentially related to migraine
KETOROLAC TROMETHAMINE	Potentially related to migraine

Generic Name	Classification
LAMOTRIGINE	Potentially related to migraine
MECLOFENAMATE SODIUM	Potentially related to migraine
MEFENAMIC ACID	Potentially related to migraine
MELOXICAM	Potentially related to migraine
MEPERIDINE HCL	Potentially related to migraine
MEPERIDINE HCL/PROMETH HCL	Potentially related to migraine
METHADONE HCL	Potentially related to migraine
METOCLOPRAMIDE HCL	Potentially related to migraine
METOPROLOL SUCCINATE	Potentially related to migraine
METOPROLOL TARTRATE	Potentially related to migraine
MIRTAZAPINE	Potentially related to migraine
MORPHINE SULFATE	Potentially related to migraine
MORPHINE SULFATE/PF	Potentially related to migraine
NABUMETONE	Potentially related to migraine
NADOLOL	Potentially related to migraine
NALBUPHINE HCL	Potentially related to migraine
NAPROXEN	Potentially related to migraine
NAPROXEN SODIUM	Potentially related to migraine
NICARDIPINE HCL	Potentially related to migraine
NIFEDIPINE	Potentially related to migraine
NIMODIPINE	Potentially related to migraine
NORTRIPTYLINE HCL	Potentially related to migraine
OXYCODONE HCL	Potentially related to migraine
OXYCODONE HCL/ACETAMINOPHEN	Potentially related to migraine
OXYCODONE/ASPIRIN	Potentially related to migraine
PAROXETINE HCL	Potentially related to migraine
PENTAZOCINE HCL/ACETAMINOPHEN	Potentially related to migraine
PENTAZOCINE HCL/NALOXONE HCL	Potentially related to migraine
PINDOLOL	Potentially related to migraine
PIROXICAM	Potentially related to migraine
PROPOXYPHENE HCL	Potentially related to migraine
PROPOXYPHENE HCL/ACETAMINOPHEN	Potentially related to migraine
PROPOXYPHENE HCL/ASA/CAFFEINE	Potentially related to migraine
PROPOXYPHENE NAPSYL	Potentially related to migraine
PROPOXYPHENE/ACETAMINOPHEN	Potentially related to migraine
PROPRANOLOL HCL	Potentially related to migraine
PROTRIPTYLINE HCL	Potentially related to migraine
RIBOFLAVIN	Potentially related to migraine
ROFECOXIB	Potentially related to migraine
SALSALATE	Potentially related to migraine
SERTRALINE HCL	Potentially related to migraine
SULINDAC	Potentially related to migraine
TIMOLOL	Potentially related to migraine
TIMOLOL MALEATE	Potentially related to migraine

Generic Name	Classification
TOLMETIN SODIUM	Potentially related to migraine
TOPIRAMATE	Potentially related to migraine
TRAMADOL HCL	Potentially related to migraine
TRAMADOL HCL/ACETAMINOPHEN	Potentially related to migraine
VALDECOXIB	Potentially related to migraine
VALPROATE SODIUM	Potentially related to migraine
VALPROIC ACID	Potentially related to migraine
VENLAFAXINE HCL	Potentially related to migraine
VERAPAMIL HCL	Potentially related to migraine

MEDICAL EXPENSE PERFORMANCE RATING SYSTEM CODES

Code	*Description*
AA	Medical Care
AAA	Internal Medicine
AAB	Cardiology
AAC	Coronary Care Unit
AAD	Dermatology
AAE	Endocrinology
AAF	Gastroenterology
AAG	Hematology
AAH	Medical ICU
AAI	Nephrology
AAJ	Neurology
AAK	Oncology
AAL	Pulmo/Resp Disease
AAM	Rheumatology
AAN	Physical Medicine
AAO	Clinical Immunology
AAP	HIV III - AIDS
AAQ	Bone Marrow Transplant
AAR	Infectious Disease
AAS	Allergy
AAX	Medical Care Cost Pool
AAZ	Medical Care NEC
AB	Surgical Care
ABA	General Surgery
ABB	Cardio/Thoracic Surgery
ABC	Surgical ICU
ABD	Neurosurgery
ABE	Ophthalmology
ABF	Oral Surgery
ABG	Otolaryngology
ABH	Pediatric Surgery
ABI	Plastic Surgery
ABJ	Proctology
ABK	Urology
ABL	Organ Transplant
ABM	Burn Unit
ABN	Peripheral Vascular Surgery

Code	Description
ABP	Head and Neck Surgery
ABQ	Vascular & Interventional Radiology
ABX	Surgical Care Cost Pool
ABZ	Surgical Care NEC
AC	Obstetrical and Gynecological Care
ACA	Gynecology
ACB	Obstetrics
ACX	OB/GYN Care Cost Pool
ACZ	OB/GYN NEC
ADA	Pediatrics
ADB	Newborn Nursery
ADC	Neonatal ICU
ADD	Adolescent Pediatrics
ADE	Pediatric ICU
ADX	Pediatric Care Cost Pool
ADZ	Pediatric Care NEC
AE	Orthopedic Care
AEA	Orthopedics
AEB	Podiatry
AEC	Hand Surgery
AEX	Orthopedic Care Cost Pool
AEZ	Orthopedic Care NEC
AF	Psychiatric Care
AFA	Psychiatrics
AFB	Substance Abuse Rehab
AFX	Psychiatric Care Cost Pool
AFZ	Psychiatric Care NEC
AG	Family Practice Care
AGA	Family Practice Medicine
AGB	Family Practice Surgery
AGC	Family Practice Obstetrics
AGD	Family Practice Pediatrics
AGE	Family Practice Gynecology
AGF	Family Practice Psychiatry
AGG	Family Practice Orthopedics
AGH	Family Practice Newborn Nursery
AGX	Family Practice Cost Pool
AGZ	Family Practice Care NEC
BA	Medical Care
BAA	Internal Medicine Clinic
BAB	Allergy Clinic
BAC	Cardiology Clinic
BAE	Diabetic Clinic

Code	Description
BAF	Endocrinology Clinic
BAG	Gastroenterology Clinic
BAH	Hematology Clinic
BAI	Hypertension Clinic
BAJ	Nephrology Clinic
BAK	Neurology Clinic
BAL	Nutrition Clinic
BAM	Oncology Clinic
BAN	Pulmonary Disease Clinic
BAO	Rheumatology Clinic
BAP	Dermatology Clinic
BAQ	Infectious Disease Clinic
BAR	Physical Medicine Clinic
BAS	Radiation Therapy Clinic
BAT	Bone Marrow Transplant Clinic
BAU	Genetic Clinic
BAX	Medical Clinics Cost Pool
BAZ	Medical Care NEC
BB	Surgical Care
BBA	General Surgery Clinic
BBB	Cardio/Thoracic Surgery Clinic
BBC	Neurosurgery Clinic
BBD	Ophthalmology Clinic
BBE	Organ Transplant Clinic
BBF	Otolaryngology Clinic
BBG	Plastic Surgery Clinic
BBH	Proctology Clinic
BBI	Urology Clinic
BBJ	Pediatric Surgery Clinic
BBK	Peripheral Vascular Surg Clinic
BBL	Pain Management Clinic
BBM	Vascular & Interventional Radiology Clinic
BBX	Surgical Clinics Cost Pool
BBZ	Surgical Care NEC
BC	Obstetrical and Gynecological Care
BCA	Family Planning Clinic
BCB	Gynecology Clinic
BCC	Obstetrics Clinic
BCX	OB/GYN Clinics Cost Pool
BCZ	OB/GYN Care NEC
BD	Pediatrics Care
BDA	Pediatrics Clinics
BDB	Adolescent Clinic

Code	Description
BDC	Well Baby Clinic
BDX	Pediatric Clinics Cost Pool
BDZ	Pediatric Care NEC
BE	Orthopedic Care
BEA	Orthopedic Clinic
BEB	Cast Clinic
BEC	Hand Surgery Clinic
BEE	Orthotic Laboratory
BEF	Podiatry Clinic
BEX	Orthopedic Care Cost Pool
BEZ	Orthopedic Care NEC
BF	Psychiatric and Mental Health Care
BFA	Psychiatric Clinic
BFB	Psychology Clinic
BFC	Child Guidance Clinic
BFD	Mental Health Clinic
BFE	Social Work Clinic
BFF	Substance Abuse Rehab Clinic
BFX	Psychiatric and Mental Health Cost Pool
BFZ	Psychiatric Clinics NEC
BG	Family Practice Care
BGA	Family Practice Clinic
BGX	Family Practice Cost Pool
BGZ	Family Practice NEC
BH	Primary Medical Care
BHA	Primary Care Clinics
BHB	Medical Examination Clinic
BHC	Optometry Clinic
BHD	Audiology Clinic
BHE	Speech Pathology Clinic
BHF	Community Health Clinic
BHG	Occupational Health Clinic
BHH	Tricare Outpatient Clinics
BHI	Immediate Care Clinic
BHX	Cost Pool
BHZ	Primary Medical Care Clinics NEC
BI	Emergency Medical Care
BIA	Emergency Medical Clinic
BIX	Emergency Medical Cost Pool
BIZ	Emergency Medical Care NEC
BJ	Flight Medicine Care
BJA	Flight Medicine Clinic
BJX	Flight Medicine Cost Pool

Code	Description
BJZ	Flight Medicine NEC
BK	Underseas Medicine Care
BKA	Underseas Medicine Clinic
BKX	Underseas Medicine Clinic Cost Pool
BKZ	Underseas Medicine NEC
BL	Rehabilitative Ambulatory Services
BLA	Physical Therapy Clinic
BLB	Occupation Therapy Clinic
BLX	Rehabilitative Ambulatory Services Cost Pool
BLZ	Rehabilitative Ambulatory Services
CA	Dental Services
CAA	Dental Care
CAX	Dental Care Cost Pool
CAZ	Dental Services NEC
CB	Dental Prosthetic
CBA	Dental Laboratory
CBX	Dental Laboratory Cost Pool
CBZ	Dental Prosthetics NEC
DA	Pharmacy Services
DAA	Pharmacy
DAX	Pharmacy Cost Pool
DAZ	Pharmacy NEC
DB	Pathology
DBA	Clinical Pathology
DBB	Anatomical Pathology
DBD	Cytogenetic Lab (AF & N Only)
DBE	Molecular Genetic Lab (AF & N Only)
DBF	Biochemical Genetic Lab (AF & N Only)
DBX	Pathology Cost Pool
DBZ	Pathology NEC
DCA	Diagnostic Radiology
DCX	Diagnostic Radiology Cost Pool
DCZ	Radiology NEC
DD	Special Procedures Services
DDA	Electrocardiography
DDB	Electroencephalography
DDC	Electroneuromyography
DDD	Pulmonary Function
DDE	Cardiac Catheterization
DDX	Special Procedures Services Cost Pool
DDZ	Special Procedures Svcs NEC
DE	Central Sterile Supply and Materiel Service
DEA	Central Sterile Supply

Code	Description
DEB	Central Material Service
DEX	Central Sterile Supply and Materiel Service Cost Pool
DEZ	Central Services NEC
DF	Surgical Services
DFA	Anesthesiology
DFB	Surgical Suite
DFC	Post-Anesthesia Care Unit
DFX	Surgical Services Cost Pool
DFZ	Surgical Services NEC
DG	Same Day Services
DGA	Same Day Services
DGB	Hemodialysis
DGD	Peritoneal Dialysis
DGE	Ambulatory Nursing Services
DGX	Same Day Services Cost Pool
DGZ	Ambulatory Procedures Visits NEC
DH	Rehabilitative Services
DHA	Inhalation/Respiratory Therapy
DHX	Rehabilitative Services Cost Pool
DHZ	Rehabilitative Services NEC
DI	Nuclear Medicine Care
DIA	Nuclear Medicine
DIX	Nuclear Medicine Cost Pool
DIZ	Nuclear Medicine NEC
DJ	Intensive Care
DJA	Medical ICU
DJB	Surgical ICU
DJC	Coronary Care Unit
DJD	Neonatal ICU
DJE	Pediatric ICU
DJX	Command, Mgmt, and Admin Cost Pool
DJZ	ICU NED
EA	Depreciation
EAA	Inpatient Depreciation
EAB	Ambulatory Depreciation
EAC	Dental Depreciation
EAD	Special Programs Depreciation
EAE	Medical Readiness Depreciation
EAZ	Depreciation NEC
EB	Command, Mgmt, and Admin
EBA	Command
EBB	Special Staff
EBC	Administration

Code	*Description*
EBD	Clinical Management
EBE	Graduate Medical Education Support
EBF	Education/Training Program Support
EBG	Peacetime Exercise/Disaster Prepare
EBH	Third Party Collection Administration
EBI	Graduate Dental Education Support
EBX	Command, Mgmt, and Admin Cost Pool
EBZ	Command, Mgmt, and Admin NEC
ED	Support Services
EDA	Plant Management - Funded/Reimburseable
EDB	Operation of Utilities - Funded/Reimburseable
EDC	Maintenance of Real Property - Funded/Reimburseable
EDD	Minor Construction - Funded/Reimburseable
EDE	Other Engineering Support - Funded/Reimburseable
EDF	Lease of Real Property - Funded/Reimburseable
EDG	Transportation - Funded/Reimburseable
EDH	Fire Protection - Funded/Reimburseable
EDI	Police Protection - Funded/Reimburseable
EDJ	Communications - Funded/Reimburseable
EDK	Other MTF Support Svcs - Funded/Reimburseable
EDX	Supt Svcs - Funded/Reimburseable Cost Pool
EE	Material Services
EEA	Material Services
EEX	Material Svcs Cost Pool
EEZ	Material Svcs NEC
EF	Housekeeping
EFA	Housekeeping
EFX	Housekeeping Cost Pool
EFZ	Housekeeping NEC
EG	Biomedical Equip Repair
EGA	Biomedical Equip Repair
EGX	Biomedical Equip Cost Pool
EGZ	Biomedical Equip Repair NEC
EH	Laundry Service
EHA	Laundry Service
EHX	Laundry Service Cost Pool
EHZ	Laundry Service NEC
EI	Nutrition Management
EIA	Patient Food Operations
EIB	Combined Food Operations
EIC	Inpatient Clinical Nutrition Management
EIX	Nutrition Management Costpools
EIZ	Nutrition Management NEC

Code	Description
EJ	Inpatient Affairs
EJA	Inpatient Affairs
EJX	Inpatient Affairs Cost Pool
EJZ	Inpatient Care Administration NEC
EK	Ambulatory Care Administration
EKA	Ambulatory Care Administration
EKX	Ambulatory Care Admin Cost Pool
EKZ	Ambulatory Care Administration NEC
EL	Tricare and Managed Care
ELA	Tricare and Managed Care Administration
ELX	Cost Pool
ELZ	Tricare and Managed Care Administration NEC
FA	Specified Health Related Programs
FAA	Area Reference Laboratories
FAB	Area Dental Prosthetic Lab
FAC	Ophthalmic Fabrication and Repair
FAD	DoD Military Blood Program
FAF	Drug Screening and Testing Program
FAH	Clinical Investigation Program
FAI	Physiological Trng/Support Program
FAK	Student Expenses
FAL	Continuing Health Education
FAM	GME Intern/Resident Expenses
FAN	GDE Intern/Resident Expenses
FAO	GME Fellowship/Resident Expenses - FT Research
FAP	GME Fellowship Expenses
FAQ	GDE Fellowship Expenses
FAX	Specified Health-Related Prog Cost Pool
FAZ	Specified Health-Related Prog NEC
FB	Public Health Services
FBB	Preventive Medicine
FBC	Industrial Hygiene Program
FBD	Radiation Health Program
FBE	Environmental Health Program
FBF	Epidemiology Program
FBI	Immunizations
FBJ	Early Intervention Services (EIS)
FBK	Medically Related Services (MRS)
FBL	Multi-Disciplinary Team Services (MTS)
FBN	Hearing Conservation Program
FBX	Public Health Svcs Cost Pool
FBZ	Public Health Svcs NEC
FC	Health Care Svcs Supt

Code	*Description*
FCA	Purchased or Referred Care
FCB	Guest Lecturer & Consultant Program
FCC	CHAMPUS Beneficiary Support
FCD	Support to Other Military Activities
FCE	Support to Other Federal Agencies
FCF	Support to Non-Federal Activities
FCG	Support to Non-MEPRS Reporting Med Active
FCH	OCONUS Emergency and Activity Duty Remote Area Care
FCZ	Health Care Svcs Supt NEC
FD	Military-Unique Medical Activites
FDB	Base Operations- Medical Installation
FDC	Nonpatient Food Operations
FDD	Decedent Affairs
FDE	Initial Outfitting
FDF	Urgent Minor Construction
FDG	TDY/TAD Enroute to PCS
FDH	Military Funded Emergency Leaves
FDI	In-place Consecutive Overseas Tour Leave
FDX	Cost Pools
FDZ	Military Unique Med Activ NEC
FE	Patient Movement and Military Patient Administration
FEA	Patient Transportation
FEB	Patient Movement Expenses
FEC	Transient Patient Care
FED	Military Patients Personnel Administration
FEF	Aeromedical Staging Facilities
FEX	Patient Movement/Admin Cost Pool
FEZ	Patient Movement/Mil Patient Adm NEC
FF	Veterinary Services
FFA	Dep Commander for Veterinary Svc
FFB	Commissary Food Inspection
FFC	Troop Issues Supply Food Inspection
FFD	Supply Point Food Inspection
FFE	Depot Food Inspection
FFF	Origin Food Inspection
FFG	Veterinary Laboratory
FFH	Animal Dz Prevention & Ctrl Facility
FFX	Veterinary Svcs Cost Pool
FFZ	Veterinary Svcs NEC
GA	Deployment Planning & Administration
GAA	Deployment Planning & Administration
GAB	Other Readiness Planning & Admin
GB	Readiness Exercises

Code	*Description*
GBA	Field or Fleet Readiness Exercises
GD	Unit or Personnel Deployments
GDA	Unit or Personnel Deployments
GE	Readiness Logistics Management
GEA	Propositioned War Reserve
GEB	Contingency Patient Care Areas
GEC	Contingency Blocks/Packs
GF	Readiness Physical Training
GFA	Readiness Physical Training
GG	National Disaster Medical System (NDMS)
GGA	NDMS Planning & Administration
GGB	NDMS Exercises

Appendix C

TRICARE DEFINITIONS OF A CLINIC AND HOSPITAL

Hospital - A health care treatment facility capable of providing definitive inpatient care. It is staffed and equipped to provide diagnostic and therapeutic services in the fields of general medicine and surgery and preventative medicine services, and has the supporting facilities to perform its assigned mission and functions. A hospital may, in addition, perform the functions of a clinic.

Clinic - A health treatment facility primarily intended and appropriately staffed and equipped to provide emergency treatment and ambulatory services. A clinic also is intended to perform certain non-therapeutic activities related to the health of the personnel served, such as physical examinations, immunizations, medical administration, preventive medicine services, and health promotion activities to support a primary military mission. In some instances, a clinic also may routinely provide therapeutic services to hospitalized patients to achieve rehabilitation goals; e.g., occupational therapy and physical therapy. A clinic may be equipped with beds for observation or patients awaiting transfer to a hospital, and for the care of patients who cannot be cared for on an outpatient status, but who do not require hospitalization. Clinic beds are not included in the "occupied-bed days" tracked by military treatment facilities.

Appendix D

COMPARISON OF INCLUDED AND EXCLUDED SUBJECTS

TABLE D.1. Comparison of Categorical Characteristics (N = 8,436)

	Included		***Excluded***		***Comparisons***	
	(n = 3,762)		***(n = 4,674)***			
Characteristic	***Count***	%	***Count***	%	d_i	χ^2
Female	3,057	81.26	3,889	83.21	-5.1	5.42*
Beneficiary Category						
Active Duty	1,040	33.59	1,053	22.53	11.8	
Other	2,722	72.36	3,621	77.47	-11.8	29.24**
Branch of Service						
Army	1,264	33.59	1,474	31.54	4.4	
Air Force	1,113	29.59	1,517	46.83	-6.2	
Navy/Marine	1,305	34.69	1,571	33.61	2.3	
Other	80	2.12	112	2.39	-1.8	9.62*
Geographic Region						
Northeast	358	9.52	395	8.45	3.7	
Mid-Atlantic	652	17.33	871	18.64	-3.4	
Southeast	457	12.15	623	13.33	-3.5	
Gulf South	320	8.51	438	9.37	-3.0	
Heartland	217	5.77	297	6.35	-2.5	
Southwest	358	9.52	495	10.59	-3.6	
Central	569	15.12	695	14.87	0.7	
Southern California	228	6.06	229	4.89	5.1	
Golden Gate	87	2.31	108	2.31	0.0	
Northwest	144	3.83	191	4.09	-1.3	
Overseas	372	9.89	332	7.11	10.0	37.18**
Treatment Facility						
Clinic	1,321	35.11	1,340	28.67	13.9	
Hospital	667	17.73	871	18.64	-2.3	
Teaching Hospital	875	23.26	1,375	29.42	-14.0	
Non-Military Facility	899	23.89	1,088	23.28	1.5	58.37**
Prescription Service						
MTF Only	1,453	38.62	1,343	28.73	21.0	
Low Retail	1,091	29.01	1,675	35.84	-14.6	
High Retail	1,218	32.37	1,656	35.43	-6.5	96.92**
Pre-Treatment Specialty Care	660	17.54	1,600	34.23	-38.8	295.96**

Note. d_i = Standardized percent difference. * p < 0.05. ** p < 0.01.

TABLE D.2. Comparison of Continuous Characteristics for Included and Excluded Subjects (N = 8,436)

	Included		***Excluded***			
	(n = 3,762)		**(n = 4,674)**		***Comparisons***	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	d_i	***t***
Age (years)	35.8	11.79	38.8	11.48	-25.2	11.5**
Pre-Treatment MSAM Use[a]	16.0	40.41	32.9	62.42	-31.4	14.4**
Pre-Treatment Comorbidity[b]	8.7	6.03	12.4	7.24	-55.1	24.9**

Note. d_i = Standardized percent difference. [a] migraine-specific abortive medication (MSAM) measured in Defined Daily Doses (DDD). [b] indicates a count of unique prescription medications received.

* p < 0.05. ** p < 0.01.

TABLE D.3. Mean Ambulatory Health Care Spending for Included and Excluded Subjects over the 18 Month Study Period (N = 8,436)

	Included		***Excluded***			
	(n = 3,762)		**(n = 4,674)**		***Comparisons***	
Characteristic	**Mean[a]**	**SD**	**Mean[a]**	**SD**	d_i	***t***
Prescription						
Definitely Migraine Related	203.42	467.51	348.69	693.53	-24.6	-10.9**
Potentially Migraine Related	181.21	474.88	519.24	874.55	-48.0	-21.3**
Total Prescription	715.38	1,865.20	1,430.64	1,951.66	-37.5	-17.1**
Non-Emergent Care						
Migraine Only	303.75	726.58	507.05	1,005.73	-23.2	-10.4**
All Cause	1,788.47	2,611.89	2,441.28	3,250.77	-22.1	-9.9**
Emergency Room Care						
Migraine Only	64.06	311.44	109.19	541.24	-10.2	-4.8**
All Cause	162.20	506.45	243.21	946.58	-10.7	-4.7**
Total Ambulatory Care						
Migraine Only	752.08	1,255.15	1,484.12	1,843.15	-46.4	-20.8**
All Cause	2,666.74	3,564.50	4,117.06	4,360.49	-36.4	-16.5**

Note. d_i = Standardized percent difference. [a] expenditures measured in unadjusted US $ expressed as per member per 180 days. * p < 0.05. ** p < 0.01.

Appendix E

PROPENSITY SCORE SPECIFICATION FOR LONGITUDINAL HYPOTHESES

TABLE E.1. Propensity Score Estimation for Longitudinal Hypotheses

Matching Variables	***Coefficient***	***Standard Error***
Age	0.017	0.022
Age Squared	$-2.4e^{-4}$	$2.8e^{-4}$
Female	0.287	0.427
Age * Gender (interaction)	-0.011	0.009
Mid-Atlantic	0.088	0.157
Southeast	0.130	0.169
Gulf South	-0.130	0.189
Heartland	0.417*	0.201
Southwest	-0.025	0.179
Central	0.053	0.166
Southern California	0.160	0.205
Golden Gate	0.444	0.267
Northwest	0.285	0.228
Overseas	0.083	0.181
Air Force	0.057	0.099
Navy/Marine Corps	-0.090	0.097
Other	0.003	0.272
Active Duty	0.556*	0.218
Active Duty * Female (Interaction)	-0.583*	0.244
Low Frequency Retail	0.454*	0.099
Hi Frequency Retail	0.377*	0.125
Hospital	0.435*	0.112
Teaching Hospital	0.451*	0.108
Non-MTF Facility	0.098	0.145
Pre-treatment Comorbidity	0.093*	0.007
Log Pre-Treatment Migraine Expenditures	-0.059*	0.017
Pre-Treatment MSAM Use	$2.2e^{-4}$	0.001
Pre-Treatment Specialty Care	0.836*	0.100
Constant	-2.351*	0.531
N (subjects)	3,762	
Log-likelihood	-2,084.02	
Pseudo-R^2	0.0982	

FIGURE E.1. Distribution of Estimated Probabilities of Exposure to Daily Migraine Prevention for Longitudinal Hypotheses

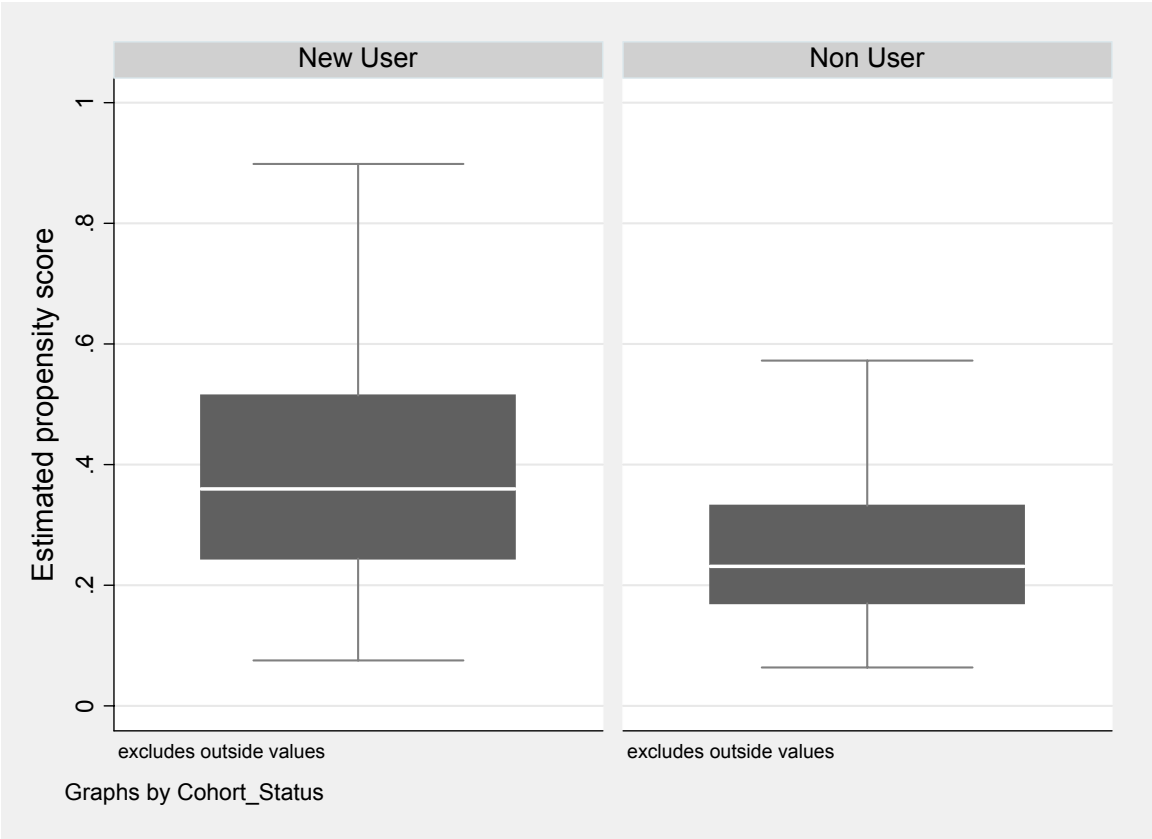


TABLE E.2. Distribution of New and Non Users of Daily Migraine Prevention and the Region of Common Support

	New Users		***Non Users***		
	(n = 1,144)		**(n = 2,618)**		***Total***
Support	**Count**	**%**	**Count**	**%**	**Count**
Off Support	147	13	0	0	147
On Support	997	87	2,618	100	3,615
Total	1,144	100	2,618	100	3,762

FIGURE E.2. Histogram of Estimated Probabilities of Exposure to Daily Migraine Prevention by Cohort Status and Region of Common Support

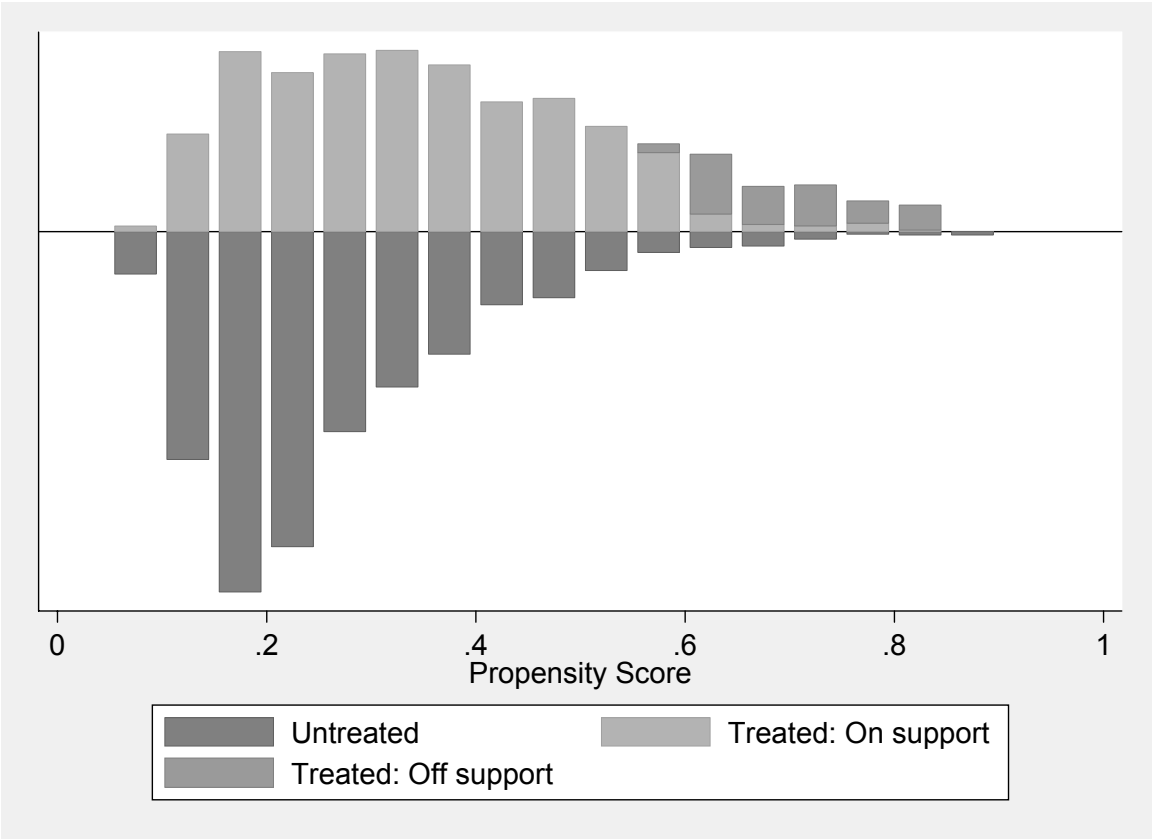


TABLE E.3. Covariate Balance after Caliper Matching for Longitudinal Hypotheses on Select Characteristics (N = 1,997)

		Covariate			***Comparisons***	
Characteristic	**Sample**	**X_t**	**X_c**	***d_i***	***d_i* percent reduction**	**Sig.**
Age	Unmatched	34.5	36.4	-16.5		***
	Matched	34.9	34.8	1.0	93.8	ns
Female	Unmatched	0.781	0.827	-11.6		***
	Matched	0.793	0.791	0.5	95.6	ns
Beneficiary Category						
Active Duty	Unmatched	0.324	0.256	15.2		***
	Matched	0.304	0.311	-1.6	89.8	ns
Treatment Facility						
Clinic	Unmatched	0.304	0.372	-14.3		***
	Matched	0.326	0.315	2.3	83.6	ns
Hospital	Unmatched	0.211	0.163	12.3		***
	Matched	0.207	0.205	0.5	95.8	ns
Teaching Hospital	Unmatched	0.307	0.200	24.7		***
	Matched	0.267	0.277	-2.3	90.6	ns
Non-Military Facility	Unmatched	0.178	0.265	-21.1		***
	Matched	0.201	0.204	-0.7	96.5	ns
Prescription Service						
MTF Only	Unmatched	0.358	0.399	-8.5		**
	Matched	0.368	0.358	2.1	75.7	ns
Low Retail	Unmatched	0.363	0.258	22.7		***
	Matched	0.326	0.339	-2.8	87.5	ns
High Retail	Unmatched	0.280	0.343	-13.7		***
	Matched	0.306	0.303	0.7	95.2	ns
Pre-Treatment Comorbidity	Unmatched	11.069	7.668	55.9		***
	Matched	9.775	9.894	-1.9	96.5	ns
Pre-Treatment Spending (ln)	Unmatched	4.788	4.521	10.2		**
	Matched	4.710	4.767	-2.2	78.6	ns
Pre-Treatment MSAM Use	Unmatched	16.407	15.799	1.4		ns
	Matched	16.323	15.804	1.2	14.6	ns
Pre-Index Specialty Care	Unmatched	0.288	0.126	40.9		***
	Matched	0.213	0.229	-4	90.1	ns
Propensity Score	Unmatched	0.390	0.267	76.3		***
	Matched	0.341	0.349	-4.6	94	ns

Appendix F

DIAGNOSTIC TESTS FOR SELECT REGRESSION MODELS

DIAGNOSTIC CHECK – Hypothesis 6 – Total Ambulatory Spending

UNUSUAL or INFLUENTIAL DATA

TABLE F.1. Studentized Residuals Greater than Two Stratified by Cohort Membership for Hypothesis Six

	Cohort Membership		
	Non User	New User	Total (%)
Studentized Residual < 2	3,633	1,050	3,633 (96.6%)
Studentized Residual >= 2	35	94	129 (3.4%)
	2,618	1,144	3,762 (100%)

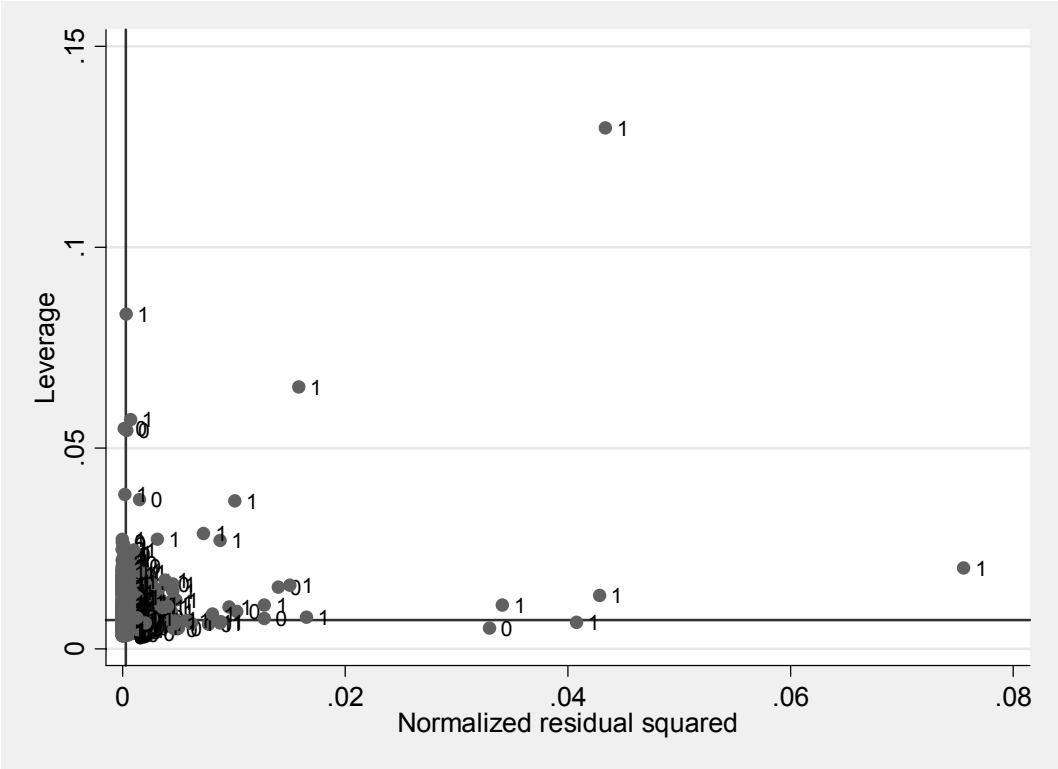
TABLE F.2. Leverage Values Greater than Twice the Mean Leverage Value Stratified by Cohort Membership for Hypothesis Six

	Cohort Membership		
	Non User	New User	Total (%)
Leverage Value < 2 * Mean	2,537	1,089	3,626 (96.4%)
Leverage Value >= 2 * Mean	81	55	136 (3.6%)
	2,618	1,144	3,762 (100%)

TABLE F.3. Belsey Kuh Welsh (BKW) Procedure Stratified by Cohort Membership for Hypothesis Six

	Cohort Membership		
	Non User	New User	Total (%)
Not Outlier by BKW Definition	2,614	1,129	3,743 (99.5%)
Outlier by BKW Definition	4	15	19 (0.5%)
	2,618	1,144	3,762 (100%)

FIGURE F.1. Leverage Plot by Normalized Squared Residual for Hypothesis Six



NORMALITY OF RESIDUALS

FIGURE F.2. Histogram of the Residuals from OLS Regression for Hypothesis Six

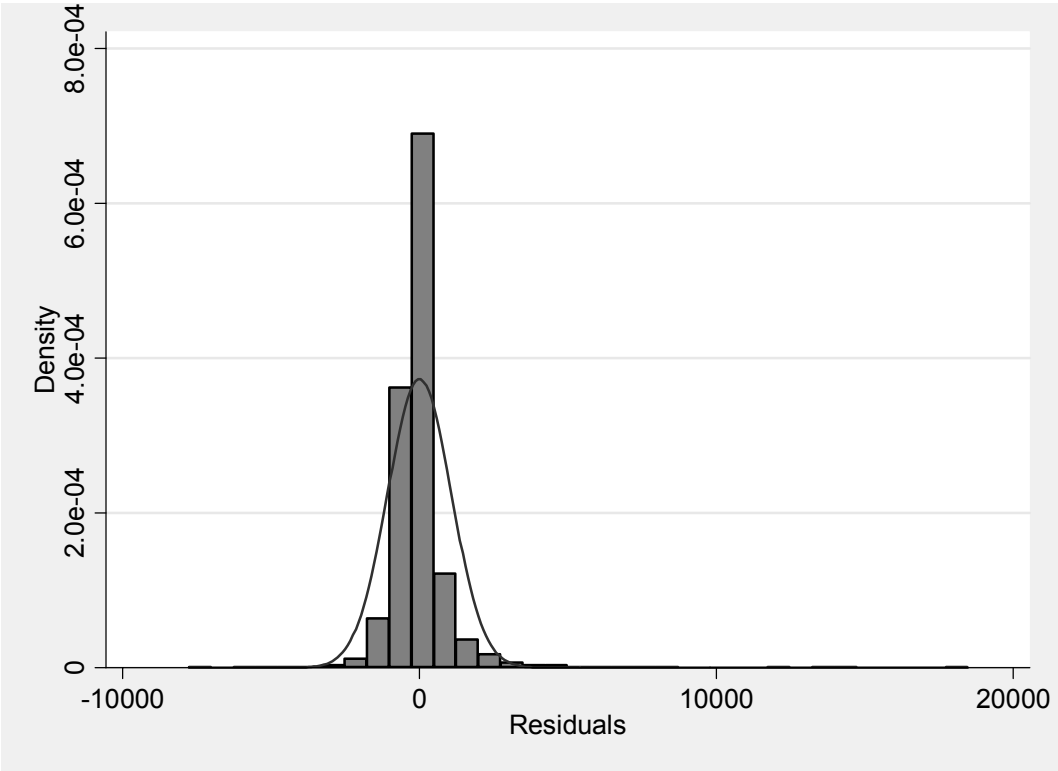


TABLE F.4. Inter-Quartile Range for Residuals after OLS Regression from Hypothesis Six

iqr r

```
   mean=  3.607           std.dev.=   1069          (n= 3762)
 median= -100.4    pseudo std.dev.=  424.6        (IQR=  572.8)
10 trim= -83.76
```

	low	high
inner fences	-1233	1058
# mild outliers	105	148
% mild outliers	2.79%	3.93%
outer fences	-2092	1917
# severe outliers	33	117
% severe outliers	0.88%	3.11%

HOMOSCEDASTICITY

FIGURE F.3. Plot of Residuals Versus Fitted (Predicted) Values from OLS Regression for Hypothesis Six

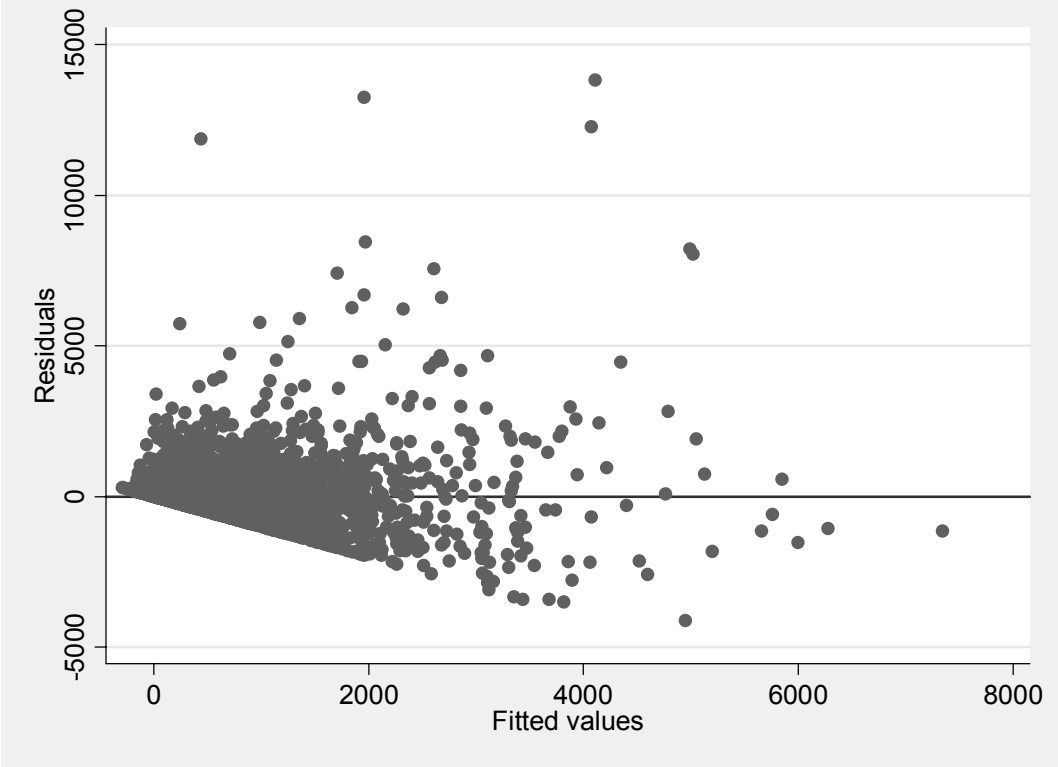


TABLE F.5. Breusch-Pagan Test for Heteroskedasticity after OLS Regression from Hypothesis Six

```
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of ha_cost_post

         chi2(1)      =  5421.78
         Prob > chi2  =   0.0000
```

DIAGNOSTIC CHECK (after transformations on trimmed sample)

NORMALITY OF RESIDUALS

FIGURE F.4. Histogram of the Residuals from Trimmed OLS Regression for Hypothesis Six

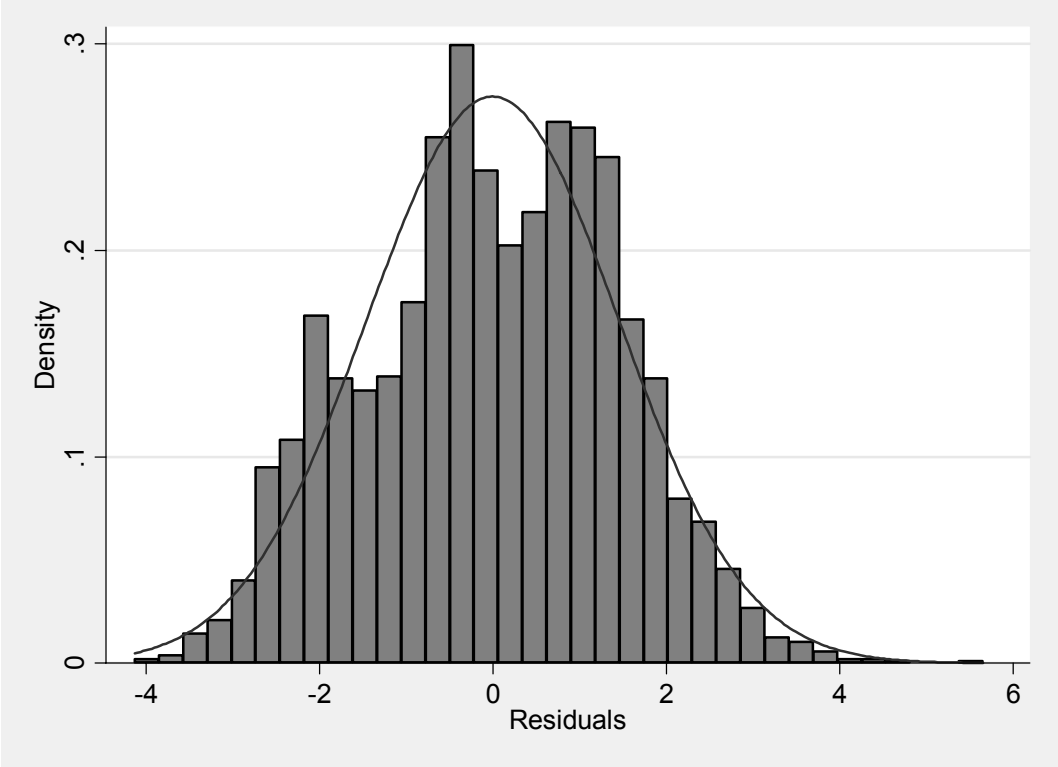


TABLE F.6. Inter-Quartile Range for Residuals after Trimmed OLS Regression from Hypothesis Six

```
   mean=  6.1e-10         std.dev.=  1.453          (n= 3762)
 median=  .0047    pseudo std.dev.=  1.539        (IQR=  2.076)
10 trim=  .0129
                                                 low         high
                                                 -------------------
                                      inner fences   -4.105       4.198
                                 # mild outliers     1           4
                                 % mild outliers     0.03%       0.11%

                                      outer fences   -7.218       7.312
                                 # severe outliers   0           0
                                 % severe outliers   0.00%       0.00%
```

HOMOSCEDASTICITY

FIGURE F.5. Plot of Residuals Versus Fitted (Predicted) Values from Trimmed OLS Regression for Hypothesis Six

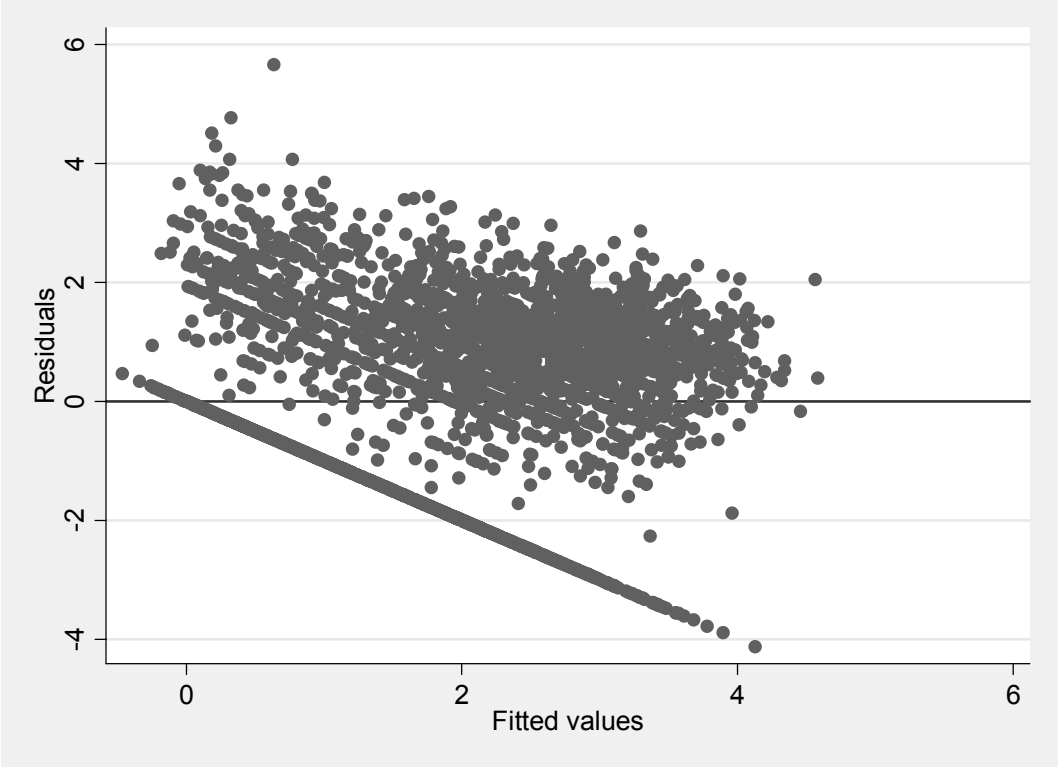


TABLE F.7. Breusch-Pagan Test for Heteroskedasticity after OLS Regression from Hypothesis Six

```
Breusch-Pagan / Cook-Weisberg test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of tdef_mig_post_ln

         chi2(1)      =     8.30
         Prob > chi2  =   0.0040
```

DIAGNOSTIC CHECK – Hypothesis 6 – Total Ambulatory Spending

UNUSUAL or INFLUENTIAL DATA CHECK AFTER TRANSFORMATION

TABLE F.8. Absolute Studentized Residuals Greater than Two Stratified by Cohort Membership for Hypothesis Six After Transformation

	Cohort Membership		
	Non User	New User	Total (%)
Studentized Residual < 2	2,549	1,098	3,647 (96.9%)
Studentized Residual >= 2	69	46	115 (3.1%)
	2,618	1,144	3,762 (100%)

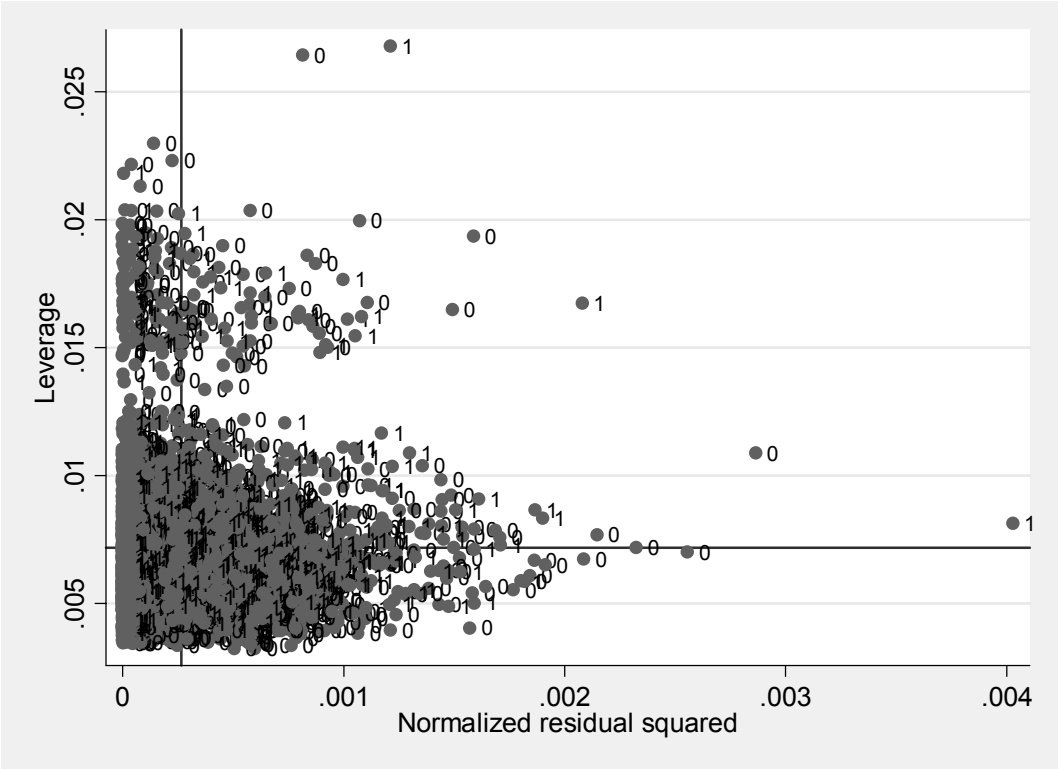
TABLE F.9. Leverage Values Greater than Twice the Mean Leverage Value Stratified by Cohort Membership for Hypothesis Six After Transformation

	Cohort Membership		
	Non User	New User	Total (%)
Leverage Value < 2 * Mean	2,538	1,108	3,626 (96.9%)
Leverage Value >= 2 * Mean	80	36	116 (3.1%)
	2,618	1,144	3,762 (100%)

TABLE F.10. Belsey Kuh Welsh (BKW) Procedure Stratified by Cohort Membership for Hypothesis Six After Transformation

	Cohort Membership		
	Non User	New User	Total (%)
Not Outlier by BKW Definition	2,614	1,141	3,743 (99.8%)
Outlier by BKW Definition	4	3	7 (0.2%)
	2,618	1,144	3,762 (100%)

FIGURE F.6. Leverage Plot by Normalized Squared Residual for Hypothesis Six After Transformation



DIAGNOSTIC CHECK – Hypothesis 12 – CHANGE IN TOTAL AMBULATORY SPENDING FROM THE TRANSITIONAL TO POST-TREATMENT INTERVAL

USUAL or INFLUENTIAL DATA

TABLE F.11. Studentized Residuals Greater than Two Stratified by Cohort Membership for Hypothesis Twelve

	Cohort Membership		
	Non User	New User	Total (%)
Studentized Residual < 2	2,584	1,030	3,633 (96.1%)
Studentized Residual >= 2	34	114	129 (3.9%)
	2,618	1,144	3,762 (100%)

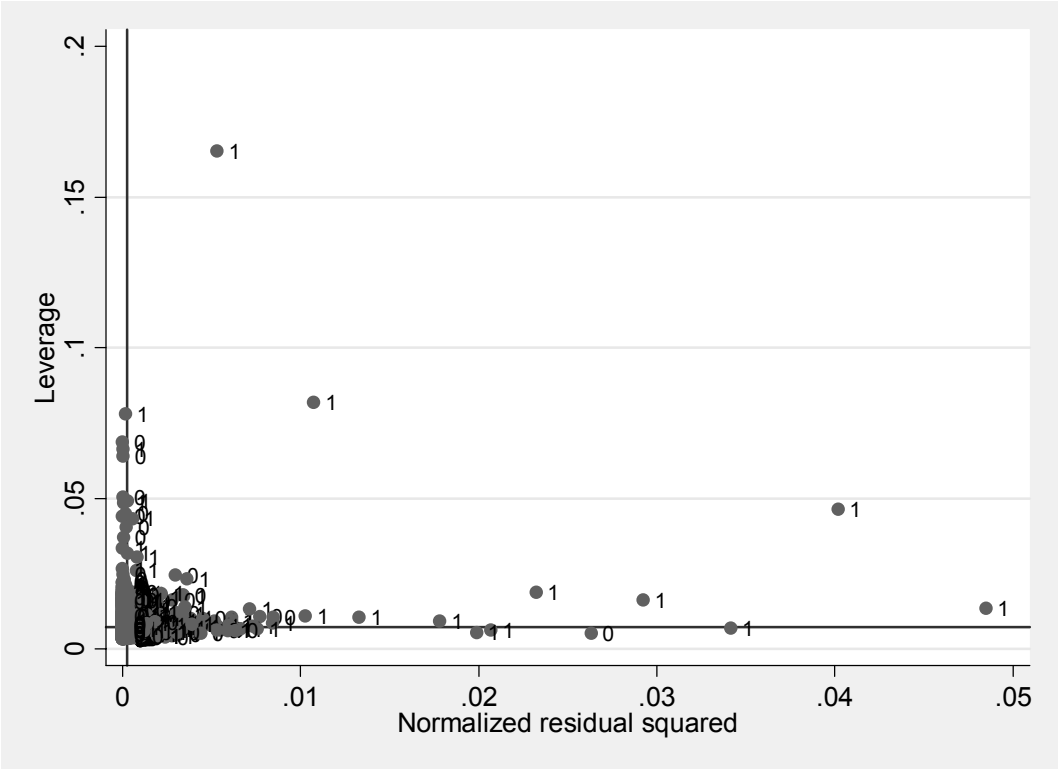
TABLE F.12. Leverage Values Greater than Twice the Mean Leverage Value Stratified by Cohort Membership for Hypothesis Twelve

	Cohort Membership		
	Non User	New User	Total (%)
Leverage Value < 2 * Mean	2,534	1,095	3,629 (96.5%)
Leverage Value >= 2 * Mean	84	49	133 (3.5%)
	2,618	1,144	3,762 (100%)

TABLE F.13. Belsey Kuh Welsh (BKW) Procedure Stratified by Cohort Membership for Hypothesis Twelve

	Cohort Membership		
	Non User	New User	Total (%)
Not Outlier by BKW Definition	2,615	1,132	3,743 (99.6%)
Outlier by BKW Definition	3	12	15 (0.4%)
	2,618	1,144	3,762 (100%)

FIGURE F.7. Leverage Plot by Normalized Squared Residual for Hypothesis Twelve



NORMALITY OF RESIDUALS

FIGURE F.8. Histogram of the Residuals from OLS Regression for Hypothesis Twelve

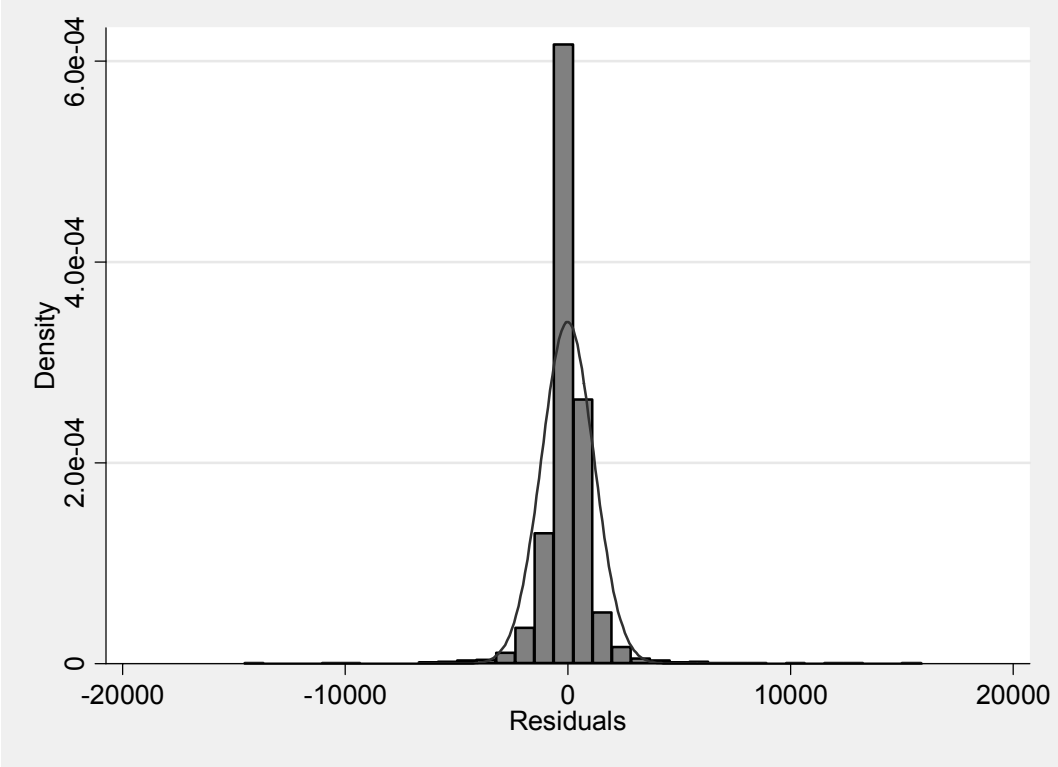


TABLE F.14. Inter-Quartile Range for Residuals after OLS Regression from Hypothesis Twelve

iqr r

```
   mean= -4.846           std.dev.=   1172          (n= 3762)
 median=  42.43    pseudo std.dev.=  486.6        (IQR=  656.5)
10 trim= -1.144
                                                low         high
                                       -------------------------
                                 inner fences    -1321         1305
                              # mild outliers    150           129
                              % mild outliers    3.99%         3.43%

                                 outer fences    -2306         2290
                              # severe outliers  81            72
                              % severe outliers  2.15%         1.91%
```

HOMOSCEDASTICITY

FIGURE F.9. Plot of Residuals Versus Fitted (Predicted) Values from OLS Regression for Hypothesis Twelve

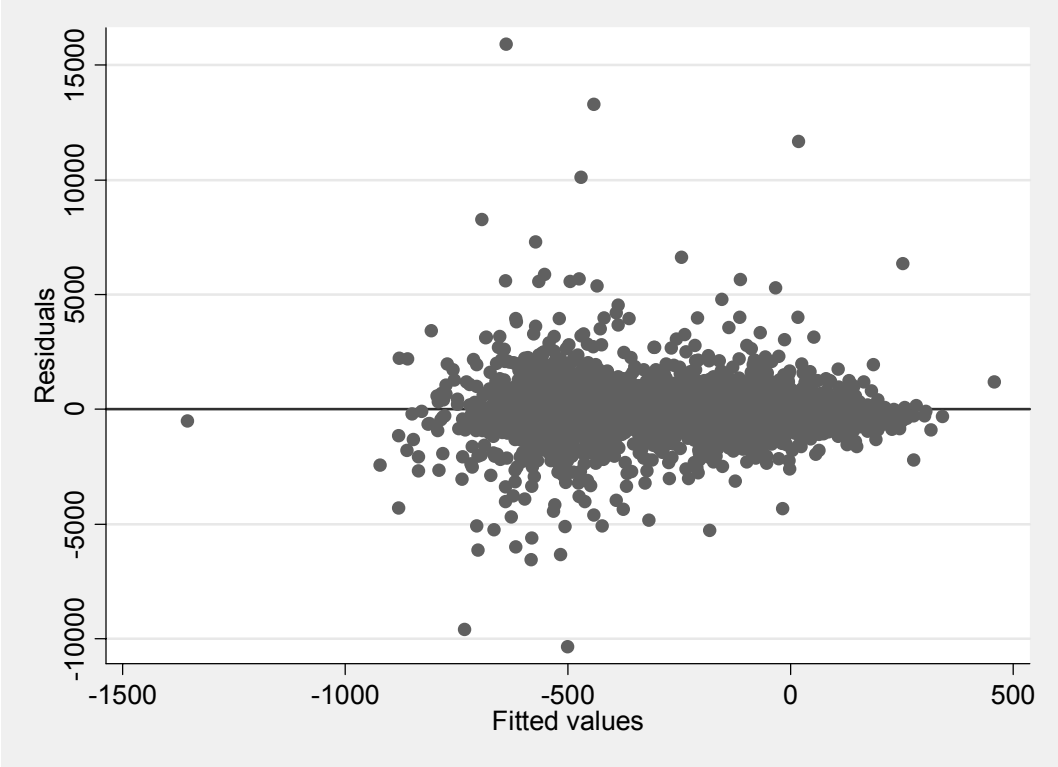


TABLE F.15. Breusch-Pagan Test for Heteroskedasticity after OLS Regression from Hypothesis Twelve

```
hettest

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity
         Ho: Constant variance
         Variables: fitted values of cs_ha_cost

         chi2(1)      =  1299.31
         Prob > chi2  =   0.0000
```